REMARKS/ARUMENTS

Upon entry of the instant amendment, claims 30, 44 and 55 will be amended, whereby claims 30-60 will remain pending. Claims 30, 44 and 55 are independent claims.

Applicants note that the claims are amended herein in accordance with discussions conducted during an October 7, 2003 interview. In particular, as will be further discussed below, during the interview cosmetic changes to the independent claims were discussed in order to even further clarify Applicant's invention as compared to the prior art. In this regard, to once again assist the Examiner's review of the claimed subject matter and its advantages over the prior art, the Examiner's attention is directed to page 2 of Applicants' specification, beginning in the first paragraph, and page 7, beginning in the fourth paragraph, wherein it is disclosed that the present invention is directed to the use of an enzyme for the manufacture of an agent for treatment and/or prophylaxis of a bacterial infection. Moreover, it is disclosed that an advantage of using a diet containing xylanase or a cellulase for rearing animals is that the amount of antimicrobial drugs which have previously been routinely incorporated in the diet can be reduced, or in some cases omitted entirely.

Reconsideration and withdrawal of the rejections of record are respectfully requested.

Discussion Of October 7, 2003 Interview

Applicants express appreciation for the courtesies extended by Supervisory Patent Examiner Brumback during an October 7, 2003 interview at the Patent and Trademark Office with Arnold Turk on behalf of the Applicants. During the interview, Applicants' specification

was thoroughly discussed, especially the disclosed advantages associated with Applicants' invention in the treatment of bacterial infections in the absence of therapeutic and/or prophylactic amounts of antimicrobial drugs. The documents of record were discussed along with additional documents to once again demonstrate the use of antimicrobial drugs in chickens to treat infections, and to demonstrate the desirability of reducing/eliminating the use of antimicrobial drugs in the diet of chickens. Still further, the advantages of Applicants' invention were discussed.

Still further, the Examiner suggested claim language to overcome the 35 U.S.C. 112 rejections. Claim language was also discussed to even further clarify Applicants' invention and the differences over the prior art. In particular, it was discussed that the claims may be amended to recite methods of treatment and/or prophylaxis of bacterial infection in chickens in the absence of therapeutic or prophylactic amounts of antimicrobial drugs, the bacterial infection caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof.

Further, it was argued that Applicants' invention is not inherently practiced in the prior art, especially because, at the time of Applicants' invention, the use of antimicrobial drugs is widespread in the prior art and, even if a compound such as xylanase was fed to chickens, Applicants' method with not be present. In this regard, it was argued that to treat bacterial infections utilizing any feed and/or combinations of feeds in the prior art of record, one having ordinary skill in the art would incorporate antibiotics at a concentration that are effective for treatment and/or prophylaxis of bacterial infection in the feeds because of the lack of any

knowledge that xylanase, cellulase, or β-glucanase has antimicrobial activity.

Also, during the interview, it was noted that the certified copy of the foreign priority application was present in the file wrapper.

The arguments and articles presented to the Examiner during the interview, and the claims as discussed with the Examiner are included in the amendment and arguments presented herein.

Request For Confirmation of Receipt Of Certified Copy

Applicants note that a certified copy of GB 9715214.4 was filed by Certificate of Mailing on December 28, 2000. **The Examiner is therefore respectfully requested to acknowledge the claim of priority under 35 U.S.C. 119 as well as receipt of the certified copy.**

Request For Return Of Initialed Form PTO-1449

Applicants filed a Second Supplemental Information Disclosure Statement on June 18, 2003; however, an initialed copy of the Form PTO-1449 was not included in the Office Action.

The Examiner is therefore respectfully requested to confirm consideration of this disclosure statement by initialing the Form PTO-1449 submitted therewith, and forwarding a copy of the initialed form with the next communication from the Patent and Trademark Office. Of course, if a copy of any information is necessary, the Examiner is respectfully requested to contact the undersigned.

Response To Restriction Requirement

Applicants confirm the election of Group I, claims 30-43, with traverse. Applicants further note that Group II, claims 44-60 stand withdrawn from further consideration by the Examiner as being drawn to a non-elected invention.

In response to the Restriction Requirement, Applicants respectfully submit that the requirement is not appropriate, because:

(a) Similarly claimed inventions including xylanase, cellulase and beta-glucanase were before the Examiner when the previous Office Actions on the merits were mailed.

(b) It is presumed that when a first Office Action on the merits is mailed that the examination is complete with respect to patentability of the invention as claimed. See 37 C.F.R. 1.104(a).

(c) A "serious burden" cannot be present when similarly claimed subject matter including the same enzymes has already received an action of the merits.

In view of the lack of a "serious burden' in the present application, and the fact that previous Office Actions on the merits have already issued in this application examining each of the enzymes, Applicants respectfully submit that a restriction requirement is not appropriate.

In view of the foregoing, it is respectfully requested that the Examiner seriously reconsider the requirement for restriction, and withdraw the same so as to give an examination on the merits on all of the claims pending in this application.

Response To Rejections Under 35 U.S.C. 112, First And Second Paragraphs

Claims 30-43 are rejected under 35 U.S.C. 112, first and second paragraphs, as failing to comply with the written description requirement and as being indefinite.

In response, Applicants note that during the above-noted interview, it was discussed that the claims are in compliance with the requirements of 35 U.S.C. 112 which was clear from the fact that the Office Action indicated an understanding of the claim language. The Supervisory Patent Examiner suggested amendments to the language to even further clarify the claim language, and indicated that these rejections would be withdrawn.

Accordingly, the suggested amendment to claim 30 has been made herein (and also to withdrawn claims 44 and 55) whereby these grounds of rejection should be withdrawn.

Response To Rejections Based Upon Prior Art

Applicants note that the following rejections are set forth in the Final Office Action:

Claims 30-43 are rejected under 35 U.S.C. 102(b) as being anticipated by GB 2,287,867 (hereinafter "GB '867"), Bedford et al., U.S. Patent No. 5,612,055 (hereinafter "Bedford '055), or Bedford et al., U.S. Patent No. 5,624,678 (hereinafter "Bedford '678")

Claims 30-43 are rejected under 35 U.S.C. 102(e) as being anticipated by Clarkson et al., U.S. Patent No. 5,902,581 (hereinafter "Clarkson") or Hansen et al., U.S. Patent No. 5,817,500 (hereinafter "Hansen").

Claims 30-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over GB '867, Bedford '055, Bedford '678, Clarkson or Hansen.

In view of the multiplicity of rejections and the similarity of the issues presented therein, and in an attempt to advance prosecution, Applicants are once again responding to the rejections by submitting a description of their invention and providing a discussion of the advantages associated with their invention. Applicants will also note the wide use of antimicrobial drugs throughout the poultry industry. Following such description and discussion, Applicants will provide a review of the prior art, and will point out the differences between their disclosed and claimed invention and the prior art of record. From this, it will be seen that Applicants' disclosed and claimed invention is not taught nor suggested by the prior art of record.

As disclosed in Applicants' originally filed specification (which claims priority of GB 9715214.4, filed July 18, 1997, and was filed as PCT/EP98/04440, on July 16, 1998), such as at page 7, beginning in the fourth paragraph, the advantage of using a diet containing xylanase or a cellulase for rearing animals is that the amount of antimicrobial drugs which have previously been routinely incorporated in the diet can be reduced, or in some cases omitted entirely. This enables considerable economic savings to be achieved in view of the relative expense of antibiotics. Moreover, in some countries where such drugs are banned, it represents a totally new approach to the control of bacterial diseases.

Moreover, as disclosed beginning in the next paragraph of Applicants' specification, omitting antibiotics from an animal's diet provides several potential further benefits. For example, it has previously been necessary to withdraw antibiotics from the animal's diet for a certain time prior to slaughter. This ensures that the meat is relatively free from such drugs and thus fit for human consumption. In contrast, according to the present invention, if antibiotics are

entirely omitted from an animal's diet, then the animal can be slaughtered at any age rather than after a certain withdrawal period. This affords the farmer improved flexibility and removes the risk of animals becoming infected shortly prior to slaughter.

Still further, as disclosed in Applicants' specification, there are economic advantages, such as the meat being marketed as being free of antibiotics. Moreover, even if the inclusion of the enzyme only enables the level of inclusion of antibiotics to be reduced, then the overall cost of controlling bacterial infection will be reduced. Synergy or potentiation of the antibiotic with the enzyme may extend the useful life of the antibiotic, such as may be due to a build up of resistance due to excessive use of the antibiotic.

As disclosed on page 2 of Applicants' specification, the paragraph beginning at the middle of the page, current methods of control of bacterial infections include the application of antibiotics, feed sterilization and careful and controlled handling and cooking of the carcass after slaughter. The application of antibiotics has proved unpopular with consumer groups wishing to reduce the quantity of potentially harmful chemicals in food. The use of antibiotics also has the problem that antibiotic-resistant strains of bacteria can be created, making such infections more difficult to treat in the future. The prophylactic use of antibiotics in animal feeds has thus been regulated in some countries effectively reducing the available methods of control.

Applicants' method has the advantage of treatment and/or prophylaxis of bacterial infection in chickens in the absence of therapeutic or prophylactic amounts of antimicrobial drugs. For example, as recited in Applicants' independent claim 30, Applicants' invention provides a method for treatment and/or prophylaxis of bacterial infection in chickens in the

absence of therapeutic or prophylactic amounts of antimicrobial drugs, the bacterial infection caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof, the method comprising:

feeding the chickens a diet which diet is effective for treatment and/or prophylaxis of bacterial infection in chickens caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof, the diet including xylanase with the xylanase being present in an amount effective for treatment and/or prophylaxis of the bacterial infection in the absence of an antimicrobial drug or in the presence of an antimicrobial drug at a concentration that in the absence of the xylanase is not effective for treatment and/or prophylaxis of bacterial infection in chickens caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof, and the diet not containing an antimicrobial drug or containing an antimicrobial drug at a concentration that is not effective in the absence of the xylanase for treatment and/or prophylaxis of bacterial infection in chickens caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof.

Applicants' method provides for the treatment and/or prophylaxis of bacterial infections in chickens while providing a beneficial reduction or elimination of antimicrobial drugs. This enables the economic advantage of reduced use or the elimination of antibiotics in the treatment of chickens. Coupled with this economic advantage is the scientific advantage of reducing the chance of creating antibiotic-resistant strains of bacteria. Moreover, the withdrawal period from

antibiotics prior to slaughter of the animals can be eliminated. Such elimination of the withdrawal period prior to slaughter is not taught or suggested in the prior art.

During the above-noted interview, Applicants discussed a number of articles which were presented with the response filed May 16, 2003 and presented several additional articles demonstrating the use of antibiotics in the poultry industry, the desire to cut back on such antibiotic use, and the ability of Applicants' invention to achieve the long felt need to reduce or eliminate antibiotics in the poultry industry. Thus, the Examiner is once again invited to review these documents and the additional documents being presented herein to see the state of the art and the beneficial advantages of Applicants' invention.

In particular, attention is once again directed to the following previously submitted articles pertaining to the use of antibiotics in animal feeds:

Burrous, "Poultry Industry Quietly Cuts Back On Antibiotic Use - Major Change In Policy" appearing in The New York Times, Sunday, February 10, 2002,

Schuff, "Reports Show Prevalence of Bacteria Contamination", Journal of Feedstuffs, Vol. 74, No. 51, December 16, 2002, pages 1 and 22.

Fenster, "Feed Additives: A Global Market Study", Animal Pharm Reports, pages 1-3 and 75-79, January 30, 2001. (Pages 1-118 are presently being submitted along with cover pages and additional back pages, and again the Examiner is specifically referred to pages 75-79.)

Moreover, attention is directed to the following articles being submitted as even further evidence of the wide use of antibiotics in animal fees, and the present desire to cut down on such use.1

Wallinga et al., Poultry on Antibiotics: Hazards To Human Health, 2nd Edition, pages ii and 1-24.

Russell, Watt PoultryUSA, Ban Antibiotics In Poultry [Why The Policymakers Have It Wrong], March 2003, pages 16-20 and 22.

BayerWatch.Com, Bayer Won't Pull Poultry Antibiotics, posted November 1, 2001.

USA, US Poultry Companies Halting Use Of Antibiotic, March 4, 2002.

Science and Technology Desk, Antibiotics In Animal Feed Debate Heats Up In The USA, published May 9, 2002.

Weisse, USA Today, High Bacteria in Poultry Raises Alarm, December 11, 2002.

Dudley-Cash, Feedstuffs, Field Research Measures Effect Of Removing GPA From Broiler Feeds, February 2003.

Tampa Tribune, Strep And Overuse Of Antibiotics, Editorial, March 13, 2003.

University of Buffalo Chemist Traces the Environmental Fate Of Antibiotics Used With Livestock From Barnyards To Crop Fields, March 25, 2003.

Gavin, London Free Press, Improper Antibiotic Use Endangers Us All, March 25, 2003.

---

1 In accordance with MPEP 609(c)(3), these documents are being submitted as evidence directed to an issue of patentability raised in an Office action for consideration in connection with arguments being made in reply to the Office action. Therefore the requirements of 37 CFR 1.97 and 37 CFR 1.98 need not be satisfied in order to have the documents considered.

Casewell et al, Advance Access published July 1, 2003, Journal of Antimicrobial Chemotherapy (2003)52, 159-161, The European Ban On Growth-Promoting Antibiotics And Emerging Consequences For Human And Animal Health.

Emery, USA. Study Finds Tainted, Drug Resistant Meats Common, October 18, 2001.

Judicious Use of Antimicrobials for Poultry Producers, August 2001, Pages 1-12 and cover page.

Moreover, attention is once again directed to the following articles, including articles by the inventors of the present application, which relate to the use of antibiotics in poultry feeds, the decision of the European Union to eliminate certain antibiotics in animal feeds, and the above-noted advantages of Applicants' invention.

Bedford, "Removal of Antibiotic Growth Promoters From Poultry Diets: Implications and Strategies To Minimise Subsequent Problems", World's Poultry Science Journal, Vol. 56, December 2000, pages 347-365.

Apajalahti et al., "Improve Bird Performance By Feeding Its Microflora", World Poultry, Elsevier Volume 15, No. 2, 1999, total of 3 pages.

Jones, "Why Chunky Chickens Are Better For Your Health", New Scientist, March 24, 2001, total of 1 page.

Bedford, "Enzymes, Antibiotics And The Intestinal Microflora", Feed Mix, Vol. 9, No. 2, 2001, pages 32-34.

Fernandez et al., "Diet Influences The Colonisation Of *Campylobacter jejuni* And Distribution Of Mucin Carbohydrates In The Chick Intestinal Tract", Cell. Mol. Life Sci., 57 (2000) 1793-1801.

Tucker et al., "Feed Enzymes And Betain In Antibiotic Free Poultry Diets", AFMA Matrix, AFMA, PO Box 4473, Rivonia 2128, South Africa, March 2000, Vol. 9, No. 1, total of 3 pages.

Danisco Press Release, "Food Poisoning Bacteria *Campylobacter* and *Salmonella* Reduced In Broilers Fed Diets Supplemented With Enzyme", August 2, 2002, total of 2 pages.

The widespread use of antibiotics in animal and poultry feeds is readily evident from the articles noted herein. In fact, these articles are recent articles with many of the articles having publication dates as late as 2002 and 2003. This is in comparison with Applicants' priority date of 1997. For example, attention is directed to the above-noted Wallinga, at pages 6 and 7, wherein the use of antibiotics in poultry and other food animals is discussed. Wallinga notes that estimates by industry and advocacy groups agree that antibiotic use in food animals is huge, as much as 29.5 million pounds, dwarfing total human use by 4 to 10-fold. It is further noted that antibiotics are put in feed not only for therapeutic purposes, but also to promote growth or to prevent infections among flocks raised in cramped, stress inducing, often hygienic conditions conductive to infection.

Still further, Applicants note that as the Examiner may be aware from the reading of newspapers that McDonalds in the United States is asking for antibiotics to be removed from meat that they purchase over the next few years.

Applicants respectfully submit that the prior art of record does not teach or suggest Applicants' invention which, as recited in independent claim 30, provides a method for treatment and/or prophylaxis of bacterial infection in chickens in the absence of therapeutic or prophylactic amounts of antimicrobial drugs, the bacterial infection caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof, the method comprising:

feeding the chickens a diet which diet is effective for treatment and/or prophylaxis of bacterial infection in chickens caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof, the diet including xylanase with the xylanase being present in an amount effective for treatment and/or prophylaxis of the bacterial infection in the absence of an antimicrobial drug or in the presence of an antimicrobial drug at a concentration that in the absence of the xylanase is not effective for treatment and/or prophylaxis of bacterial infection in chickens caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof, and the diet not containing an antimicrobial drug or containing an antimicrobial drug at a concentration that is not effective in the absence of the xylanase for treatment and/or prophylaxis of bacterial infection in chickens caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof.

Moreover, the prior art of record does not teach or suggest, as recited in Applicants' independent claim 44, a method for treatment and/or prophylaxis of a bacterial infection in chickens in the absence of therapeutic or prophylactic amounts of antimicrobial drugs, the

bacterial infection caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof, the method comprising:

feeding the chickens a diet comprising a feed including a cellulase and at least about 25% by weight of a cereal selected from the group consisting of wheat, maize, rye, barley, oats, triticale, rice, sorghum and mixtures thereof, the diet being effective for treatment and/or prophylaxis of bacterial infection in the chickens caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof, and the cellulase being present in an amount effective for treatment and/or prophylaxis of the bacterial infection in the absence of an antimicrobial drug or in the presence of an antimicrobial drug at a concentration that in the absence of the cellulase is not effective for treatment and/or prophylaxis of bacterial infection in chickens caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof, and the diet not containing an antimicrobial drug or containing an antimicrobial drug at a concentration that is not effective in the absence of the cellulose for treatment and/or prophylaxis of bacterial infection in chickens caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof.

Still further, the prior art of record does not teach or suggest, as recited in Applicants' independent claim 55, a method for treatment and/or prophylaxis of a bacterial infection in chickens <u>in the absence of therapeutic or prophylactic amounts of antimicrobial drugs</u>, the bacterial infection caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof, the method comprising:

feeding the chickens a diet comprising a feed including a β-glucanase and at least about 25% by weight of wheat, the diet being effective for treatment and/or prophylaxis of bacterial infection in the chickens caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof, and the β-glucanase being present in an amount effective for treatment and/or prophylaxis of the bacterial infection in the absence of an antimicrobial drug or in the presence of an antimicrobial drug at a concentration that in the absence of the β-glucanase is not effective for treatment and/or prophylaxis of bacterial infection in chickens caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof, and the diet not containing an antimicrobial drug or containing an antimicrobial drug at a concentration that is not effective in the absence of the β-glucanase for treatment and/or prophylaxis of bacterial infection in chickens caused by bacteria selected from the group consisting of *Salmonella*, *Campylobacter*, *Clostridium perfringens*, and mixtures thereof.

Still further, the prior art of record does not teach or suggest the subject matter of Applicants' dependent claims. For example, <u>the prior art of record does not teach or suggest the diet being fed to chickens without a withdrawal period prior to slaughtering of the chickens</u>.

The prior art does not teach or suggest any method for <u>treatment and/or prophylaxis of bacterial infection</u> in chickens <u>in the absence of therapeutic or prophylactic amounts of antimicrobial drugs</u>. In the prior art, there is absolutely no teaching or suggestion that bacterial infection in chickens can be treated without the use of therapeutic and/or prophylactic amounts of antimicrobial drugs. Moreover, one having ordinary skill in the art without the knowledge of Applicants'

invention would use therapeutic and/or prophylactic amounts of antimicrobial drugs in the diet of chickens when performing a method for treatment and/or prophylaxis of bacterial infections in chickens. Thus, Applicants' method is not inherent in the prior art.

With regard to inherency, the Examiner is reminded that in order for inherency to be present the Examiner has the burden of showing that the result indicated by the Examiner is the necessary result, and not merely a possible result. In re Oelrich, 212 U.S.P.Q. 323 (CCPA 1981); Ex parte Keith et al., 154 U.S.P.Q. 320 (POBA 1966). The fact that a prior art article may inherently have the characteristics of the claimed product is not sufficient. Ex parte Skinner, 2 U.S.P.Q.2d 1788 (BPAI 1986).

As the Board of Patent Appeals and Interferences states in Ex parte Levy, 17 U.S.P.Q.2d 1461, 1463:

> However, the initial burden of establishing a prima facie basis to deny patentability to a claimed invention rests upon the examiner. In re Piasecki, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984). In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. In re King, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986); W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983); In re Oelrich, 666 F.2d 578, 212 USPQ 323 (CCPA 1981); In re Wilding, 535 F.2d 631, 190 USPQ 59 (CCPA 1976); Hansgirg v. Kemmer, 102 F.2d 212, 40 USPQ 665 (CCPA 1939).

With the above in mind, Applicants once again note that Applicants' method would not be practiced in the prior art of record, because the prior art methods of treatment and/or prophylaxis of bacterial infection in chickens would be practiced in the presence of therapeutic or prophylactic

amounts of antimicrobial drugs. In accordance with MPEP 2112.02, Applicants' invention is directed to new and unobvious uses of compositions disclosed in the prior art.

GB '867

In contrast to Applicants' invention and as previously noted by Applicants, GB '867 discloses the use of a xylanase for assisting livestock to digest protein and/or amino acids present in a feed. GB '287 discloses that such a use increases the protein and amino acid digestibility of the livestocks' diet. Moreover, it is disclosed that such a use enables the actual protein content of feed to be reduced by including lower levels of relatively costly protein supplements, such as fishmeal and meatmeal. Still further, it is disclosed that the use enables the content of energy supplements present in the feed to be reduced from the amounts conventionally used without reducing the feed's nutritional value.

GB '867 is silent with respect to treating bacterial infections in chickens. In this regard, as noted in Applicants' originally filed specification and as supported by the above-noted articles, antibiotics are utilized in the diets of chickens to treat bacterial infections caused by bacteria. There has been a long felt need to reduce or eliminate antibiotics from the diets of chickens when treating bacterial infections; however, until Applicants' invention, the art has not been able to treat bacterial infections in chickens without using doses of antibiotics at a concentration that are effective for treatment and/or prophylaxis of bacterial infection.

Applicants note that it appears that GB '867 is silent with respect to the use of antimicrobial drugs in the feed disclosed therein. However, the question is not whether GB' 867 is silent with respect to the use of antibiotics, because GB '867 is not directed to treatment and/or

prophylaxis of antibacterial infections. As noted above, one having ordinary skill in the art would add therapeutic or prophylactic amounts of antimicrobial drugs to the diet of chickens fed the feed of GB '867 for treatment and/or prophylaxis of antibacterial infections in chickens fed the feed of GB '867.

Accordingly, GB '867 does not teach or suggest Applicants' disclosed and claimed invention.

Bedford '055

Similarly, Bedford '055 is directed to an enzyme feed additive comprising (i) a xylanase; (ii) a protease; and optionally (iii) a β-glucanase wherein the ratio of the units of xylanase activity per g of the feed additive to the units of β-glucanase activity per g of the feed additive is 1:0-0.25. Bedford '055 discloses that it has been found that the inclusion of the disclosed enzyme feed additive in the diet of an animal enables the animal to digest the diet more efficiently. Thus, it is disclosed that the addition of the additive to a feed increases the proportion of feed protein and energy which the animal can derive from the feed, and that this in turn improves the FCR of the feed making it more economical in use. Bedford '055 does disclose in Example 3 that a starter feed was used for days 0-7 that did not include antibiotics, anticoccidial or any enzyme. However, Bedford '055 does not teach nor suggest Applicants' invention, because Bedford '055 does not teach or suggest any method for treatment and/or prophylaxis of bacterial infection in chickens in the absence of therapeutic or prophylactic amounts of antimicrobial drugs. As noted above, one having ordinary skill in the art without the knowledge of Applicants' invention would

use therapeutic and/or prophylactic amounts of antimicrobial drugs in the diet of chickens when performing a method for treatment and/or prophylaxis of bacterial infections in chickens.

Accordingly, Bedford '055 does not teach or suggest Applicants' disclosed and claimed invention.

Bedford '678

Bedford '678 is directed to a method of use, and a composition, of a carbohydrase and/or a protease for the manufacture of an agent for the treatment and/or prophylaxis of coccidiosis. The agent can be in the form of a cereal-based animal feed. The carbohydrase may be a polysaccharidase such as a xylanase or a cellulase e.g., β-glucanase. Moreover, the agent may include conventional non-enzymic anticoccidial agents. Thus, Bedford '678 is directed to the treatment of coccidiosis, which is a disease which results from an infection of the digestive tract by parasitic protozoa of the order Coccidia. Bedford '678 is silent with respect to <u>treatment and/or prophylaxis of bacterial infection</u> in chickens <u>in the absence of therapeutic or prophylactic amounts of antimicrobial drugs</u>. As noted above, one having ordinary skill in the art without the knowledge of Applicants' invention would use therapeutic and/or prophylactic amounts of antimicrobial drugs in the diet of chickens when performing a method for treatment and/or prophylaxis of bacterial infections in chickens.

Accordingly, Bedford, '678 does not teach or suggest Applicants' disclosed and claimed invention.

Clarkson

Clarkson discloses beginning at column 2, line 30 that here is now a substantial body of evidence showing that incorporating certain (supplementary) enzymes in cereal-based animal feeds can be advantageous in reducing the viscosity of material present in the animal's gut. It is disclosed that this reduction can be achieved by enzymes such as xylanases which hydrolyse soluble xylans thereby reducing digesta viscosity which is an important constraint on the process of digestion.

Clarkson further discloses that the use of enzyme supplements, such as xylanase, in animal feed is complicated by the processing requirements for grain supplements. It is disclosed that often, such enzyme supplements are obtained by impregnating the enzyme onto a physiologically acceptable carrier, such as a cereal, and the impregnated carrier is mixed with the other components of the feed and then pressed into cubes or pellets for feeding directly to animals. It is disclosed that the processes which have been developed make use of relatively high temperatures to improve the efficiency of the manufacturing process and to produce feeds which are free from harmful bacteria, particularly Salmonella. It is also disclosed that the use of high temperatures improves the quality and durability of the resulting cubes and pellets, increases the range of ingredients which can be efficiently handled and also increases the level of liquid ingredients, such as fat and molasses, which can be incorporated into the feed.

It is further disclosed that unfortunately the high temperature and high pressure processing conditions characteristic of expander and pelleting technology, particularly when applied in the moist conditions normally encountered during pelleting, are potentially destructive

to certain feed components, such as any enzymes, including xylanases, which are present. Thus, it is disclosed that the prior art enzymes have generally had the problem that they are not sufficiently stable under the processing conditions of commercial pelleting operations to allow economical use of such pelleting techniques, and Clarkson is improving upon the xylanase that is being used.

Clarkson does not teach nor suggest Applicants' invention including <u>treatment and/or prophylaxis of bacterial infection</u> in chickens <u>in the absence of therapeutic or prophylactic amounts of antimicrobial drugs</u>. Again, it is noted that one having ordinary skill in the art without the knowledge of Applicants' invention would use therapeutic and/or prophylactic amounts of antimicrobial drugs in the diet of chickens when performing a method for treatment and/or prophylaxis of bacterial infections in chickens.

Accordingly, Clarkson does not teach or suggest Applicants' disclosed and claimed invention.

Hansen

Hansen is directed to improved feed enhancing enzymes which have excellent thermostability in order that the feed enhancing enzymes can be incorporated into feed under conditions preventing microbial infections in the feed. Hansen does not disclose that his thermostable feed enhancing enzymes have any antimicrobial activity when administered in a chicken diet.

Expanding upon the above, Applicants note that Hansen discloses, beginning at column 1 line 64, that:

> According to the present invention it has now been found that when compared to conventional feed enhancing enzymes, the xylanase derived from Thermomyces lanuginosus is an excellent feed enhancing enzyme which shows significant improvement of the feed utilization when added to animal feed. Moreover, owing to an excellent thermostability, the xylanase preparation derived from Thermomyces lanuginosus is particularly well suited for being processed into feed additives at conditions preventing microbial infections, in particular Salmonella infection. It has also been found that the xylanase derived from Thermomyces lanuginosus exerts a significant reduction of digesta viscosity, which indicates a significant improvement in the chicken feed conversion efficiency.

Following the disclosure of Hansen, one having ordinary skill in the art would understand that the xylanase disclosed by Hansen can be processed into feed at conditions that prevent microbial infections in the feed itself. Hansen does not teach nor suggest Applicants' invention of <u>treatment and/or prophylaxis of bacterial infection</u> in chickens <u>in the absence of therapeutic or prophylactic amounts of antimicrobial drugs</u>. Again, it is noted that one having ordinary skill in the art without the knowledge of Applicants' invention would use therapeutic and/or prophylactic amounts of antimicrobial drugs in the diet of chickens when performing a method for treatment and/or prophylaxis of bacterial infections in chickens.

Accordingly, Hansen does not teach or suggest Applicants' disclosed and claimed invention.

Obviousness Rejection

Regarding the obviousness rejection, Applicants note that the rejection is without sufficient basis. In this regard, it is noted that the rejection asserts that it would have been obvious to use the specific amounts claimed since it is well within the purview of the skilled artisan to optimize the desired results through routine experimentation. However, the rejection does not point to what amounts are being referenced, what desired results are being optimized, and what experimentation is being utilized.

Still further, Applicants note that a particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In the instant situation, the rejection does not establish any variable as a result-effective variable, and does not indicate what experimentation is considered to be routine for this variable.

Thus, if this ground of rejection is maintained, the Examiner is respectfully requested to set forth the basis of the rejection. Of course, if the basis for the rejection is stated, it would be expected that the next rejection not be made final.

In view of the above, the rejections of record should be withdrawn.

CONCLUSION

For the reasons advanced above, Applicants respectfully submit that all pending claims patentably define Applicants' invention.

Allowance of the application with an early mailing date of the Notices of Allowance and Allowability is therefore respectfully requested.

Should the Examiner have any further comments or questions, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully Submitted,
Michael R. BEDFORD et al.

Arnold Turk
Reg. No. 33,094

November 18, 2003
GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191

FEED ADDITIVES:

A GLOBAL MARKET STUDY

ANIMAL PHARM

Reports

SR 194

[BLANK PAGE]

ANIMAL PHARM Reports

FEED ADDITIVES: A GLOBAL MARKET STUDY

BY

DR ROGER FENSTER

Animal Pharm Reports publishes an extensive range of animal health product sector market reports, detailed analyses of the market for specific geographic areas, in-depth profiles of companies operating in the industry, financial and statistical analyses, and other strategic reports in the animal health sector. If you need a report whether it be market oriented, technology based, regulatory or general reference, please contact our UK-based Customer Helpdesk or one of the other offices below for further information.

UK

Animal Pharm Reports
18/20 Hill Rise
Richmond
Surrey
TW10 6UA, UK
Tel: (+44) 020 8948 3262
Fax: (+44) 020 8332 8992
(+44) 020 8948 6866

US

PharmaBooks Ltd
1775 Broadway
Suite 511
New York
NY 10019, US
Tel: (+1) 212 262 8230
Fax: (+1) 212 262 8234

JAPAN

T Hirata
Engineering Information Service Co Ltd
(Shiryo Kenkyujo Co Ltd)
3-5-20-405 Sotokanda
Chiyoda-ku
Tokyo 101-0021, Japan
Tel: (+81) 3 3258 9207
Fax: (+81) 3 3258 9209

KOREA

Pharma Koreana Ltd
Hyecheon Building
831 Yeoksam-dong
Kangnam-ku
Seoul 135-792
Korea
Tel: (+82) 2 554 9591
Fax: (+82) 2 557 1290

CONTENTS

LIST OF TABLES

EXECUTIVE SUMMARY

This market study reports on the worldwide market of feed additive use, sales turnover and manufacturing companies.

The main market segments are nutritional feed additives with an annual turnover of €3,080 million (equivalent to $3,283 million), of which amino acids accounted for 55% and vitamins for 38%, respectively.

Digestive enhancers that include antibiotic performance enhancers, enzymes, probiotics and prebiotics are valued at €1,236 million ($1,317 million). Antibiotic performance enhancers represent the largest group with 73% of segment sales. Although relatively small in turnover, a healthy growth is projected for the other groups of digestive enhancers.

Auxiliary substances comprise of a multitude of different products with a wide variety of functions. A large number of companies are involved in this segment, resulting in an incalculable number of products. Sales turnover is estimated at €911 million ($971 million). Carotenoids and organic acids capture the lions share of 52% and 25%, respectively.

Finally, disease-preventing agents are valued at €456 million ($485 million). Although infestation with coccidiosis is widespread amongst most animals, the bulk of the anti-protozoal agents are consumed by the poultry industry.

The growth rate of feed production is projected at 2–3% per annum until 2004. The prices for important feed additives are expected to recover from the all time low of 1999–2000. Overall, an annual increase of 3–4% in feed additive sales is projected for the next five years.

ABBREVATIONS

ai	active ingredient
BHA	butylated hydroxylanisole
BHT	butylated hydroxytoluene
BMD	bacitracin methylene disalicylate
BSE	bovine spongiform encephalopathy
CCN	cerebrocortico necrosis disease
CIS	Community of Independent States (former USSR)
GMO	genetically modified organism
HCl	hydrochloride
IU	international units
MFA	medicinal feed additives
MHA	methionine hydroxy analogue
MNB	menadione nicotinamide bisulphite
MPB	menadione dimethyl pyrimidinol bisulphite
MSB	menadione sodium bisulphite
MSBC	menadione sodium bisulphite complex
MSG	monosodium glutamate
NSP	non-starch-polysaccharides
OBM	organically bound mineral
ppm	parts per million
R&D	research and development
USP	United States Pharmacopeia
ug	microgram
WHO	World Health Organisation

CHAPTER 1
FOREWORD

It is appropriate to note that conducting this market research study of feed additives was extremely difficult. Much of the business information is exceptionally sensitive and confidential. The break up of several cartels in the vitamin, amino acid and organic acid industries throughout the past few years has helped in generating more market transparency. Nevertheless, companies still consider data on product sales and price developments as highly confidential. Moreover, companies are often owned by holding firms which makes gaining access to company data even more challenging.

A year was spent reviewing available information in order to provide a concise review of the market. Information was obtained by interviewing producers and end-users, studying business reports and other published industry sources and consulting manufacturers. An enormous amount of data was obtained through the author's own database FEEDADDSEARCH which compiles market information on feed additives from 1985. All market information available up to and including the third quarter of 2000 has been included, ensuring that this report represents the latest and most accurate data available.

1.1 Definition and scope

The objective of this report is to access the producers, product formulations, prices and applications of the feed additives market. Products included are additives with defined chemistry or, in case of microorganisms, of defined microbial species. Inclusion levels range between a few micrograms per tonne of feed to concentrations of below 1%. In exceptional cases, concentrations can be higher. A historical review and outlook for the coming five years elaborates on business developments and identifies scenarios on future strategies. For the more important products price developments are reviewed for the past 10 years. Since prices vary throughout the year, they are expressed as weighted average prices for a particular year. Maximum and minimum prices within a given year can vary significantly from the average figure. Particularly within the last few years, strong price fluctuations have been observed. Wherever possible, the lowest prices found in the market are also recorded for the past two years.

Company sales turnovers are given in the local currency of the producing company. Product sales are recorded in the currency of the country from where the feed additive is traded. This is mostly in dollars or German Marks.

To accomplish the objectives of this report, companies were researched, industry representatives were contacted, R&D activities were reviewed and industry publications were screened. The work covers a period of more than 10 years continuous research in the field of feed additives.

In 1995, the feed additive market was estimated to be worth $5,180 million (Colegrave & Wesley, 1995[1]). Aventis recently reported a slightly lower figure of $5,000 million although no detail was given regarding the scope of products and definition of the product range. Within this market research study the quantity and sales turnover of defined feed additives

[1] *Colegrave T & Wesley T (1995). The Feed Additives Market: Performance enhancement and disease control. Animal Pharm SR 145. Richmond: PJB Publications Ltd.*

are reviewed. In contrast to feeding stuffs, feed additives are substances which are incorporated into compound feed not to add energy, complex protein or major minerals, but for a multitude of different purposes. Desired effects of supplementing feed additives are:

- To lift the concentration of a particular nutrient to a desired level
- To affect the metabolism of the animal
- To improve and conserve the quality of compound feed
- To act on the digestion of mass feeding stuffs
- To enhance feed intake
- To enhance the pigmentation of animal products
- To beneficially influence the hygiene of the production chain
- To prevent certain diseases

It is important to understand that this report presents the individual sales turnover for each type of feed additive. In some cases, the category of feed additives is not clear. For example, organic acids can be used to preserve harvested grains and feeds, to enhance digestion, to stimulate feed intake and to add taste and flavour. Therefore, the split of product according to use-category is difficult to assess.

For modern animal production a nutritional well-balanced diet is vital. If any essential nutrient is deficient or marginally deficient, animal productivity is below optimum and health may be put at risk. Today, it is common practice to supplement compound feeds with straight nutrients to optimise a nutritionally complete feed. It is therefore not surprising that the category of nutritionals forms the major portion of sales turnover nor that research is concentrated on this category.

Feed additives are grouped according to the following categories:

- Nutritionals – straight nutrients that complement the nutritional value of a blend of feeding stuffs to complete a specific dietary requirement. These include vitamins, amino acids, accessory feed additives, trace elements and organically bound minerals

- Auxiliary substances – additives that modify the quality of the feed, improve the quality of food derived from animal production, change the physical-chemical characteristic of feed, improve the palatability of feed or reduce exposure to disease causing agents. These include carotenoids, antioxidants, taste and flavour substances, emulsifiers, organic acids, anticaking agents, ammonia binders, mycotoxin binders and pellet binders

- Digestive enhancers – feed additives that act on the gastrointestinal tract to improve the digestive capability. Products comprise of antibiotic growth enhancers, probiotics, prebiotics, enzymes and feed additives of plant origin

- Disease preventing agents– Medicinal feed additives that are used to prevent and control microbial diseases. This category includes anticoccidials and antihistomonals

All the products listed above are commonly accepted and used in modern animal feeds. Additives are generally applied in feed mills and premix factories. They are also used by companies which produce speciality feeds such as liquid preparations.

1.2 Animal production

There are several factors which are extremely favourable for the expansion of animal production throughout the next years. Firstly, world economic growth for 2000 is estimated at about 4%. In 2001, a figure above 3% is again projected. The longterm outlook is positive for a sustained economic growth in all global areas. World population will grow slightly above 1% per annum. This and the increase in available income of consumers will further increase demand for meat, milk and egg products.

Compound feed production in the year 1999 is estimated to be close to 600 million tonnes. Production growth is projected at 2–3% per annum till 2004. Major factors that will influence growth are:

- Low cost of major feed raw materials
- The World Trade Organisation fostering fair agricultural trade
- Most Asian countries showing a fast recovery from the 1997/1998 crisis
- The CIS countries, Middle East and Africa growing at healthy rates
- The pig industry set to recover in Europe and to substantially expand in China and the Americas

Global compound feed consumption is broken down by production segments in Table 1.1. The largest segment is represented by poultry feed. Both layers and broilers account for 34% of all feed consumed. Pigs hold the second position followed by cattle. The aquaculture segment represents 5%. Although still small in percentage, fish and shrimp feed was by far the fastest growing sector in the past 10 years. In future, this segment will continue to outperform the other feed categories in terms of growth rate.

Table 1.1: Global feed use in 1999 – split of production segments

Production segment	%
Pig feed	33
Broiler feed	25
Dairy cattle feed	17
Layer feed	9
Beef cattle feed	8
Feed for aquaculture species	5
Other feeds	3

Over the next five years the following projections are made for the single animal production segments:

- Poultry production will grow between 3% and 4%. Expansion of production will occur all over the world. Major growth in volume will be seen in North and Latin America, in Europe and in Asia

- The excess supply of pigs in many countries in the years 1998 and 1999 has forced meat prices down. Many farmers have reduced or even terminated production. The slow price recovery in 1999 will encourage the pig industry to increase production

again. In Asia, a 3% growth per annum is estimated. The industry in Europe will grow at about 1% and in the Americas at almost 2%

- Beef cattle production is projected to gradually decrease. The growing consumer preference for white meat and the consumer's concern about bovine spongiform encephalopathy (BSE) disease are depressing consumption. Milk production will grow at 1.5% per annum till 2004. Driving forces are the growing consumption of cheese and milk powder and the increasing population

- The aquaculture feed market is the fastest growing market segment. Annual growth is estimated above 5%. Increasing demand comes mainly from seawater fish and shrimp. If disease problems with Asian shrimp farming can be successfully overcome, an additional 2–3% growth is projected

1.3 Value of feed additives

The global sales value at ex-manufacturers level in 1999 is estimated at

€ 5,680 million, equivalent to

$ 6,054 million

The largest segment in the feed additives business is the group of nutritional products. This group generates more than 54% of all feed additive sales. The second largest segment is the group of digestive enhancers, followed by the auxiliary substances (see Table 1.2). The largest single product is methionine, which represents almost 19% of all sales.

Table 1.2: Feed additive categories - Sales split in 1999

Product category split	%
Feed additive segment	
Nutritionals	54
Auxiliary substances	16
Digestive enhancers	22
Disease preventing agents	8

Many key products suffered a rapid decline in price throughout 1999 and early 2000. Having reached an all time low in 1999, prices for methionine and lysine are now recovering. The case is the same for several vitamins. Biotin and vitamin E prices seem have already recovered. Other additives are still sliding down the pricing scale.

The amino acids business is dominated by a handful of companies. Major producers are Mitsui/Novus, Aventis, Degussa, ADM and Ajinomoto. Aventis, Degussa and ADM have additional major business interests in the vitamin sector. Growth rates for amino acids are estimated at 5% per annum throughout the next five years. If environmental concern about animal waste in general and nitrogenous contamination in water, soil and air in particular accelerates, a growth rate of above 5% is realistic.

The future vitamin business is influenced by two major factors. One is growing competition from Chinese companies, which have already entered the market for most vitamins. Today,

Chinese manufacturers already offer vitamins A, E, C, pantothenic acid, B_1, B_2, B_6, B_{12}, folic acid, niacin and D_3. The second factor is the termination of the illegal price fixing cartel of the leading manufacturers. Unlike the past 10 years when prices were kept artificially high, true competition is now back in place. Manufacturers are now trying to find their market position within the new competitive environment. The over-reaction in price decreases for some vitamins is seen as part of a long-term, market-share driven strategy that aims to eliminate some of the traditional producers.

Vitamin E, the number two sales product in vitamins, is only one example in the portfolio of feed additive products, which has undergone dramatic changes in the last year. In 1997, the average price was more than DM 30 per kg, but in early 2000, the price dropped to DM 11 Importation of vitamin E from Chinese producers to Europe has almost come to a standstill. Affected by the industry consolidation, Merck announced that biotin production would be cancelled by the end of 2000. The decision was taken after prices fell by more than 50% at the end of 1999 although prices are now slowly climbing again. Takeda, another traditional player in the vitamin industry, has entered into a joint venture with world number two vitamin manufacturer BASF. Uncompetitive production costs combined with a strong local currency forced Takeda to give away its business to a stronger partner.

Management at Aventis announced in May 2000 that the animal nutrition business is no longer part of its core strategy and it is anticipated that it will divest their nutrient product line soon. More companies are expected to abandon or sell their vitamin businesses in 2001.

The market for digestive enhancers is still dominated by antibiotics. This business is expected to further decrease over the next five years due to reluctance of authorities to register new products. In addition, consumers and EU authorities have expressed their growing concerns about the risk of human antibiotic resistance, leading to the withdrawal of several products. The use of enzymes, probiotics, prebiotics and botanical feed additives will therefore take over part of this business. The growth rate for alternative digestive enhancers is projected to be above 10%. Whether the alternative products can completely replace antibiotics is still to be demonstrated so any projection carries a lot of uncertainty.

The anticoccidial and antihistomonal market is driven by the expansion of the poultry market. The increase in volume turnover will be compensated by decreasing prices at a similar percentage level. Hence, sales turnover will stabilise or even fall slightly through 2004. Overall, the sales volume for feed additives is expected to increase by 3–4% per annum till 2004. The driving forces are the growth in feed production by 2–3% and some recovery of prices for important feed additives from their lowest ever in 1999/2000.

1.4 Feed additive manufacturers

Table 1.3 lists the top 10 commercial feed additive companies for the year 1999. The ranking list is expected to change for the year 2000 because several acquisition and merger activities have taken place in the meantime.

Alpharma has acquired Roche's entire medicinal feed additive line. As combined sales for 1999, were just under €400 million, it is anticipated that it will step up in the year 2000 ranking list. Depending on the outcome of Pfizer's divestment activities, the company may lose their 1999 position. The friendly take-over of Takeda's feed additive business by BASF will strengthen the number two position of the company ahead of Aventis. Aventis has

announced that the animal nutrition business is no longer part of their core strategy, but it is not clear at this stage whether the activities are to be sold, merged or spun off.

Table 1.3: Sales turnover of main feed additive manufacturers in 1999

Sales turnover	€ million	$ million
Feed additive manufacturer		
Hoffmann-La Roche	1,300	1,220
BASF	770	821
Aventis	551	587
Mitsui/Novus	469	500
Eli Lilly	394	420
Degussa-Huels	350	373
Pfizer	338	360
ADM	188	200
Alpharma	171	182
Ajinomoto	163	174

Following a period of continuous growth by major feed additive suppliers over almost 10 years, selected products started to decline in price in 1996. Price erosion cumulated in 1999 and early 2000 when several important feed additives faced the lowest price levels since 1990. Consequently, giant feed additive manufacturers are suffering decreasing profit margins or even losses.

The break-up of several illegal price fixing cartels within the few last years has led to this unhealthy market development. The companies involved are leading manufacturers of vitamins, amino acids and organic acids. Six of the leading vitamin companies have been ordered to pay in excess of €1,000 million criminal fines. Roche, being the initiator of illegal price fixing and market allocations in the vitamin case, was fined $500 million by the US Justice Department in May 1999. Several cases are still pending.

The top 10 companies represent a combined sales turnover of €4,694 million. They account for a share of 83% of the total feed additive business. This figure represents a minor over-estimation, since premixing activities and sales of speciality products are included in the sales revenues of some companies, including Roche, BASF, Aventis and Alpharma. An estimated market share of 80% for the top 10 companies is considered to be more realistic.

CHAPTER 2
FEED ADDITIVES

Feed additives include all substances, which are added in small amounts to compound feed, speciality feeds and liquid preparations. They require no prescription from veterinarians.

2.1 Nutritional feed additives

This subcategory of feed additives includes all micro-constituents of the diet that perform specific functions in the metabolism of the animal and are chemically defined as nutritive effects. Nutritional feed additives may be offered in a pre-active or active form.

2.1.1 Vitamins

Vitamins and provitamins are organic compounds distinct from protein, fat and carbohydrate which are required in minute amounts in the feed. As animals cannot synthesise most vitamins they must be regularly supplied in the feed. Insufficient amounts will impair health, normal tissue development, maintenance and growth. Excessive supply of several vitamins causes hyper-vitaminosis.

Vitamins A, E, D_3 and K_3 are fat-soluble, B group vitamins and vitamin C are water-soluble. All products are available in dry powder form. Average particle size and particle number per gram of product are the most important physical characteristics for mixability of the micro-nutrients in compound feed. Products differ in their granulometry (variability in particle size).

Some vitamins are very sensitive to physicochemical factors such as heat, presence of metal catalysts, acid or alkaline, light and humidity. These factors may decompose or deactivate the vitamin. The most sensitive are therefore protected by methods of compaction, coating, embedding in an organic matrix, chemical stabilisation, or by forming stable derivatives of the vitamin. All processing and storage of feed results in some reduction of vitamin activity. The extent of the reduction depends on the vitamin and the particular processing conditions.

Table 2.1 lists some typical dry powder formulations.

Table 2.1: Typical vitamin product formulations – dry products

Active ingredients	Description
Vitamin A	Stablilised in a matrix of gelatin glycerin and carbohydrates with addition of antioxidant
Betacarotene	Dispersed in a starch-coated matrix of gelatin and carbohydrates with addition of antioxidant
Vitamin D_3	Dispersed in a matrix of plant protein and dextrin
Vitamin E	Adsorbed on silica or spray-dried fine granular powder of vitamin E dispersed in a matrix of gelatin and dextrin
Vitamin K_3	Crystalline powder
Vitamin B_1	Fine granular powder of thiamin mononitrate or hydrochloride
Vitamin B_2	Fine crystalline powder or spray-dried granular powder
Vitamin B_6	Fine crystalline powder
Vitamin B_{12}	Fine powder of vitamin B_{12} diluted in limestone
Niacin	Granular powder or fine crystalline powder
Calcium pantothenate	Powder of calcium D-pantothenate
Biotin	Fine Powder of d-biotin dispersed in a dextrin matrix or simple triturate
Folic acid, (folate)	Fine crystalline powder or spray-dried granular powder of folic acid in a dextrin matrix
Vitamin C	Fine crystalline powder, powder of fat or ethyl cellulose-coated ascorbic acid or powder dilution of phosphate esters

2.1.1.1 Vitamin A (retinol)

Vitamin A is essential for:

- Healthy lining of respiratory, digestive and reproductive tracts
- Healthy skin, hair coat and nerves
- Resistance to various infectious diseases
- Night vision

. . . source

Vitamin A only occurs naturally in animal organisms. Provitamin A (or betacarotene) is found in plants. Vitamin A or retinol in its alcoholic form is prone to oxidation. The typical vitamin A form in feed grade formulations is the esterified retinyl-acetate or retinyl-palmitate. Lack of vitamin A or its pro-vitamin in the feed leads to the development of typical deficiency symptoms, such as keratinisation of mucous membranes, night blindness, uncoordinated movement, raised cerebrospinal fluid pressure, hydrocephalus and increased incidence of infections.

The vitamin content of foods is expressed in international units (IU). One IU of vitamin A is equivalent to 0.344 µg vitamin A acetate.

. . . application

Vitamin A is supplemented in the compound feed of basically all animal species. Commercial vitamin A preparations are protected against oxidation and other influences that may impair the vitamin activity. The vitamin is best protected against loss of activity by embedding the retinyl ester in an organic matrix. The addition of an antioxidant provides further chemical stability.

. . . forms and formulation

The leading commercial products are offered in a granule form of 250–600μm in diameter. The particle size is relatively coarse in comparison with most other feed additives. Without the sophisticated product formulation, most of the vitamin activity would be lost during the pelleting, expansion or extrusion stages of processing.

To save on cost, vitamin A is usually formulated together with vitamin D_3 which is also unstable and fat-soluble. Concentration of vitamin A is generally 500,000 IU per gram of product. Higher product concentrations of 650,000 IU per gram are offered to the American market. For liquid preparations, water miscible formulations are available.

Inclusion rates in complete feed generally range from 4,000 to 12,000 IU per kg.

. . . market

Since investment for a sophisticated vitamin A processing plant are enormous, the main suppliers are anticipated to maintain their dominant position in the market. In view of the limited number of suppliers, significant further price erosion is unlikely despite the ample amount of vitamin A presently available in the market. Global sales are worth approximately DM 616 million.

Table 2.2: Price development for vitamin A feed grade product, 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
DM/500 × 10^6 IU	36.20	43.00	52.20	52.10	51.80	52.00	39.00

*Note: * First quarter*

. . . companies

The global market for vitamin A in the feed industry for 1999 is given in Table 2.3. The four main manufacturers cover approximately 90% of the market. Additional suppliers come from Japan, Russia, India and China. Roche which is the number one supplier, started a joint venture for the production of vitamin A with Shanghai No. 6 Pharmaceutical Factory (Roche Taishan-Shanghai – Vitamin Products) at the end of 1999. BASF, the number two manufacturer is involved in a similar joint venture activity with Northeast General Pharmaceutical Factory in Shenyang.

Table 2.3: Market share of vitamin A manufacturers, 1999

Global market	7,300 × 10^{12} IU
Manufacturer	**% market share**
Roche	49
BASF	29
Aventis	21
Others	1

Since the end of the price-fixing cartel between the main manufacturers, the price level for vitamin A shows a downwards trend. In early 2000 prices did not recover despite price increase announcements from major manufacturers. At the end of 1999, vitamin A was selling at DM 37.00. Half a year later, generic material was offered at an even lower price of DM 33.00 per kg. Corresponding prices in the US are around $20.00 for the 650 IU product concentration.

2.1.1.2 Betacarotene (provitamin A)

Betacarotene is essential for supplying a precursor molecule for the formation of vitamin A and a number of studies suggest it may be of use in other areas. Supplementation of dairy cow feed with betacarotene was shown to have beneficial effects such as increased intensity of oestrus, less follicular cysts and improved conception rate. Studies in breeding horses, sows and rabbits indicate a similar effect on fertility parameters but results are so far inconclusive.

In shrimp production, feeding of betacarotene results in a pinkish pigmentation of the exoskeleton. Evidence for essential nutritional functions is not yet available. The manufacturing companies of the provitamin do not promote the colouring effect to avoid jeopardising sales of the pigment astaxanthin.

. . . source

Generally the feed additive product originates from chemical synthesis and is a granular product with 10% activity. Like feed grade vitamin A, betacarotene is embedded in an organic matrix that protects the highly reactive carotenoid.

. . . market

Unlike most vitamins, the majority of betacarotene is sold to the food and pharmaceutical industries. Most of the scientific studies of betacarotenoids were conducted in the German speaking areas of Europe, which explains why the largest feed market for betacarotene is located in central Europe.

Prices were kept relatively stable over the past 10 years. Only recently a small downward trend has been noted. In the US, the price fluctuated around $750–$800 per kg active ingredient.

Table 2.4: Price development of betacarotene, 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
DM/kg ai°	980	1040	1100	1090	1100	1120	980

*Note: *First quarter; °active ingredient*

. . . companies

The two betacarotene producing giants, Roche and BASF, dominate the market. Typical products carry a 10% concentration. Alternative products from the fermentation process and algae cultivation are also available but these natural products do not play an important role in the market.

The global market was worth DM 17.6 million in 1999. Roche covered two thirds of the market, and BASF one third. The products of both suppliers are comparable in terms of activity and quality.

Table 2.5: Market share of feed-grade betacarotene manufacturers, 1999

Global Market, kg	17,000
Manufacturer	**% market share**
Roche	64
BASF	33
Others	3

2.1.1.3 Vitamin D

Vitamin D is essential for:

- Absorption of calcium in the digestive tract
- Metabolism of calcium and phosphorus
- Formation of bone, teeth and other connective tissue

Vitamin D supplementation in dairy cattle before parturition may prevent hypercalcaemia during lactation.

. . . source

In nature vitamin D occurs mostly as ergocalciferol or vitamin D_2 and as cholecalciferol or vitamin D_3. Vitamin D_2 is predominantly vegetable in origin and vitamin D_3 is only produced by animals. All vitamin D forms have a steroid nucleus in common and differ only in respect to their side chain. All vitamin D precursors found in feeding stuffs exhibit no direct vitamin, or anti-rachitic activity, until the ring structure is opened by ultraviolet irradiation.

In the 1960s, a new area of vitamin D_3 research began when it was found that the biological actions of vitamin D could be explained by hormone-like functions. Through hydroxylation processes in the kidney and liver several hydroxy-vitamin D_3 compounds are formed which show a similar mode of action to steroid hormones.

. . . application

Less than 100 IU per kg of bodyweight is sufficient for the prevention of bone disorders.

Proportionally young growing animals have the highest demand. Generally, all animals kept in confinement must obtain vitamin D_3 through their feed. Free ranging ruminants do not require a supplement.

. . . forms and formulations

The commercial chemical form of vitamin D is cholecalciferol. Its activity is usually expressed in IUs of vitamin D_3. One IU is equivalent to 0.025 µg of vitamin D_3. Conversely, 1mg cholecalciferol corresponds to 40'000 IU vitamin D_3. IUs are sometimes referred to as

USPs (United States Pharmacopeai) in the US. Scientific literature expresses all vitamin D_3 in weight units.

Vitamin D_3 is soluble in oil and fat solvents. In the unprotected form it is destroyed by light, oxygen and mineral catalysts.

Commercial products are formulated by spray-drying or embedding technique. Both fine powder and granular products are offered on the market. Powder formulations mostly contain 500,000 IU vitamin D_3 per gram of sales product, but products with lower concentrations are also available. Antioxidants are included in the product formulation to protect the active vitamin against oxidation. Vitamin D_3 is also offered with vitamin A as a combination product. The formulation in an organic matrix is similar to that of vitamin A. The concentrations of the combined vitamins are 500,000 IU/g for vitamin A and 100,000 IU/g for vitamin D_3, giving a ratio of 5:1. In North America 650 IU/g vitamin A to 325 IU/g vitamin D_3 is commonly used.

. . . market

Three mid-European companies cover the world market without serious competition. It is no surprise then, that the price level for vitamin D_3 has not changed much in recent years, though it has weakened slightly since 1998.

Table 2.6: Price development of vitamin D_3, 1990–2000

Year	**2000***	**1999**	**1998**	**1997**	**1996**	**1995**	**1990**
DM/kg ai	22.00	22.50	25.80	23.40	23.60	24.00	19.40

*Note: *First quarter*

. . . companies

The Dutch chemical company, Solvay (which has merged its pharmaceutical division with that of Duphar), is the leading supplier of the fat-soluble vitamin. Together with the two giant vitamin manufacturers, Roche and BASF, the global market was worth DM 90 million in 1999. Solvay's turnover equalled approximately DM 44 million. Roche, the second largest supplier, enjoyed a turnover of approximately DM 34 million. Products are mostly marketed as commodities. Differences in product quality are slight and do not play an important role in the purchasing decision.

Table 2.7: Market share of vitamin D_3 manufacturers, 1999

Global market,	1990×10^{12} IU
Manufacturer	**% market share**
Solvay	49
Roche	38
BASF	13
Others	<1

2.1.1.4 Vitamin E

Vitamin E is essential for:

- Normal function of skeletal muscles, heart muscle and liver
- Protection of body tissue and cells from oxidative destruction
- Normal function of cell membranes

Vitamin E is a generic term, which represents all molecules with biological activity of alpha-tocopherol. Feeding stuffs contain eight different alpha-tocopherol vitamers. Four tocopherols and four tocotrienols are used in commercial feed.. All vitamers are d-stereo isomers. The most potent vitamer is the d-α-tocopherol, which is used as a standard form and against which all other isomers are compared. The d-α-tocopherol provides 70–90% of all naturally available vitamin E from cereal-based complete feeds. Other tocopherol isomers, although common in most plants, show little vitamin E activity. These low potent isomers are generally ignored as a supply source of vitamin E for commercial feeds.

. . . forms and formulations

Pure vitamin E is added to feed in synthetic form. It is prepared by coupling trimethylhydroquinone with isophytol. The final product is dl-α-tocopheryl acetate, which comprises of eight different isomeric forms. Each of the non-esterified isomers has a specific biological activity, varying from 29%–100% (d-α-tocopherol=100).

The supplementation of vitamin E is commonly expressed in terms of gram-units of dl-α-tocopheryl acetate. Even in the US vitamin E quantities are often referred to as IUs rather than USPs. The quantitative definition is 1 IU vitamin E = 1mg dl-α-tocopheryl acetate.

Vitamin E is added to all types of feed. Different nutritional and health claims associated with its use mean inclusion rates vary. Addition levels generally range between 20 and 100mg per kg of complete feed.

Products supplied by the industry are:

- Adsorbate form with 50% ai dominantly used for compound feed
- Spray-dried form with 50% ai; water-dispersible product for use in milk replacers, dispersible multi-vitamin mixtures, chemically reactive mineral premixes
- Oily form: for liquid preparations

The usual form, vitamin E adsorbate, does not differ much in quality between the major suppliers. It is marketed as a commodity product.

. . . market

The global market has grown dramatically over the past decade. Percentage growth rates were well above market growth in feed production. Roche and BASF invested a lot in intramural and extramural research to elaborate scientific arguments for higher supplementation levels. Subsequently, multiple use levels in feed have been promoted.

Naturally derived vitamin E, although present in the market, has not had any great financial impact on the industry. Four major manufacturers dominate the global market for synthetic vitamin E. Illegal price fixing meant that from 1990 price levels rose 50% from around DM 20.00 to around DM 30.00 per kg of vitamin E. Until 1997 prices were kept stable, but with the break-up of the cartel, prices steadily eroded by about 60% to DM 11.30–12.50 at the beginning of 2000. In the US vitamin E sold at prices as low as $6.00. By end of the first quarter of 2000, prices seem to have reached their lowest level. Several manufacturers have since officially announced a price increase to DM 15.00.

The global market for feed grade vitamin E was worth DM 659 million in 1999. Two years earlier, the value of the global market was about 60% higher.

. . . companies

Several companies, mainly from Europe, have entered into strategic alliances with Chinese producers of vitamin E over the past few years. Companies such as Helm, Lohmann, Röthel, Neuber, Olesen and Impextraco imported vitamin E oil from China and changed it by simple formulation process into feed grade powder form. Some companies have given up production due to uncompetitive purchase prices of vitamin E oil; others remain in the market hoping for a fast recovery in the price of the powder product.

Table 2.8: Price development of vitamin E, 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
DM/kg, 50%	12.50	18.30	25.90	30.40	29.30	29.10	20.10

*Note: * First quarter*

Roche as the largest manufacturer of vitamin E is enjoying a market share of approximately 41%. In second place comes BASF with an estimated share of 24%.

Table 2.9: Market share of vitamin E manufacturers, 1999

Global Market,	18,000 tonnes
Manufacturer	**% market share**
Roche	41
BASF	24
Esai	12
Aventis	11
Others	12

2.1.1.5 Vitamin K

Vitamin K is essential for

- Normal blood clotting
- Bone formation

. . . source

Vitamin K is a collective name for a group of 2-methyl-1, 4-naphthoquinone compounds. Phylloquinone (vitamin K_1) is synthesised in plants. Menaquinones (vitamin K_2) is of bacterial origin. The commonly used form of vitamin K in animal nutrition is vitamin K_3 (menadione). Several menadione derivatives are available for supplementation to animal feed. All commercial products come from chemical synthesis.

. . . application

Vitamin K_3 is generally added to the compound feed of monogastric animals to overcome rare cases of deficiency. Scientifically, it is widely accepted that animals can cover at least part of their vitamin requirement by microbial synthesis in the lower digestive tract. Absorption of the nutrient occurs either through digestion of bacterial cells or through coprophagy. Ruminants are independent of external supply. They have the ability to cover their requirement through the synthesis of rumen bacteria.

. . . forms and formulations

All three of these vitamin K forms are fat-soluble. Menadione is highly unstable and causes skin and mucosa irritations. Therefore, water-soluble derivatives of menadione were developed for use in feed applications. Products are claimed to exhibit better stability and be less harmful for humans to handle. Feed grade products show varying degrees of vitamin K activity. Controversy surrounds the bioactivity of different products and there is ongoing debate between the commercial sector and the scientific community. The four major product forms available are shown in Table 2.10.

Table 2.10: Major product forms of vitamin K

MSB	menadione sodium bisulphite	contains 51–52% menadione
MSBC	menadione sodium bisulphite complex	contains 33% menadione
MPB	menadione dimethyl pyrimidinol bisulphite	contains 43–45% menadione
MNB	menadione nicotinamide bisulphite	contains 43% menadione

Special formulations such as coatings or adsorbate forms result in lower menadione activities. Differences in biological activity on a weight to weight basis can be best related to the menadione content of the particular products. Therefore, product prices are best compared per gram of menadione.

Stability tests indicate differences between the retention rates of vitamin K_3 in commercial products. Processing procedures and storage conditions can reduce vitamin K_3 retention to nothing, the only vitamin more unstable is vitamin C.

. . . market

One can see from the Table 2.11 that prices for vitamin K_3 remained fairly stable over the past 10 years. Prices are recorded for the MSB product type as it is the most generally used and therefore taken as the standard vitamin form. Recently, additional suppliers came to the market, which may impact on pricing of the vitamin in future.

Table 2.11: Price development of vitamin K_3, 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
DM/kg menadione	33.00	33.40	33.60	33.50	33.60	34.00	30.00

*Note: * First quarter*

Value-wise, the global sales of feed grade vitamin K_3 were DM 36 million in 1999.

. . . companies

The chemical synthesis of vitamin K_3 is generally left to smaller companies as the low-cost production is offset by the formation of highly polluting by-products (see Table 2.12). Safe dumping of the pollutants is costly and conflicts with environmental policies of the major companies.

Table 2.12: Market share of vitamin K_3 manufacturers, 1999

Global Market	550 tonnes
Manufacturer	**% market share**
Vanetta	60
Heterochemical Cooperation	28
Olpesa	5
Others	7

2.1.1.6 Vitamin B_1

Vitamin B_1 is essential for

- Metabolism of fats, carbohydrates and amino acids
- Efficient utilisation and release of energy
- Functioning of nerves, brain and muscles

. . . source

Rich natural sources of vitamin B_1 (thiamine) are by-products of the milling industry, extracts of oilseed, yeast and milk products. Thiamine supplements are added to the feed of all animals except ruminants.

. . . application

Supplementation may be advisable in growing and fattening cattle under intensive feeding conditions, or if the cattle herd have a history of cerebrocortico necrosis disease (CCN).

Deficiency symptoms in animals may occur in the presence of thiaminase. This antagonistic enzyme can be brought into the compound feed by particular feeding stuff. The presence of the enzyme destroys the active vitamin before reaching the site of digestive absorption. Such cases are mostly reported for fish feed and in fur-bearing animals that feed on fish silage.

. . . forms and formulations

Vitamin B_1 addition rates for land-based animal feeds are mostly in the range of 1g–5g per tonne of complete feed. Fish feed is supplemented with up to 12g and recommended levels for shrimp feed is as high as 80g per tonne of feed. The reason for such high supplementation levels is explained by the leaching of soluble vitamins from the feed. After placing the feed into the water, shrimp will take half an hour or more for consumption. During this time soluble nutrients dissolve in the surrounding water and are lost.

Commercially available products are thiamine monohydrate and thiamine hydrochloride (HCl). The vitamin activity of the monohydrate form is slightly higher with 92%. The HCl form carries approximately 89% thiamine activity. As it has lower solubility in water, thiamine mononitrate is mostly used in feeds for aquaculture species which reduces leaching rate and therefore loss of vitamin activity to the surrounding water.

. . . market

Prices fell when the Chinese manufacturers entered the market in the second half of the 1990s (see Table 2.13). The two market leaders, Roche and Takeda, followed the price trend from Chinese manufacturers for some time. After some significant loss of world market share, both companies changed their strategy in 1996. They became more aggressive on price aiming to regain their global share.

Table 2.13: Price development of vitamin B_1, 1990–2000 °

Year	2000*	1999	1998	1997	1996	1995	1990
DM/kg	33.20	33.00	37.00	36.50	33.10	51.00	73.00

*Note: ° combined price for the HCl and mononitrate form; * first quarter*

The global market for vitamin B_1 in feed application is approximately 970 tonnes. By taking the total production of this particular vitamin into account, feed use is estimated at only 48%.

. . . companies

Roche is the undisputed market leader in vitamin B_1 production (see Table 2.14). Roche's plant in Grenzach, Germany is to be expanded in 2000 and its capacity is anticipated to rise from 2,000 tonnes to 3,200 tonnes per annum. While some large and small manufacturers of vitamin B_1 have given up their production during the past few years, several Chinese manufacturers are withstanding the global price pressure and remain in the market.

Table 2.14: Market share of vitamin B_1 manufacturers in 1999

Global Market	970 tonnes
Manufacturer	**% market share**
Roche	60
Takeda	22
Others	18

2.1.1.7 Vitamin B_2

Vitamin B_2 is essential for:

- Repair of tissue
- Efficient utilisation of energy
- Healthy vision, skin and hair

Vitamin B_2 (riboflavin) functions as a coenzyme in several enzymatic reactions. It is required for the utilisation of fats, carbohydrates and amino acids. It is instrumental in the energy transaction of electrons in biological oxidation-reduction reactions. Riboflavin is present in the cells of all plants and animals.

. . . source

Commercial sources of vitamin B_2 come from chemical synthesis (Roche) and fermentation processes (BASF). A new fermentation plant in Grenzach, Germany opened in October 2000. The fermentation process will achieve a production capacity of 3,000 tonnes of vitamin B_2. The riboflavin will be derived from genetically modified microorganisms. The plant has been built to replace facilities in Grenzach and Fukuroi Japan, which produced the vitamin by chemical synthesis. The new fermentation process, is predicted to reduce production costs from DM 50 to DM 24 per kg.

. . . application

Ruminants with a functional rumen do not require vitamin B_2 supplementation. The synthesis of the vitamin by rumen microbes is sufficient to cover the required amounts. Monogastric animals require the addition of riboflavin to feed. Typical supplementation levels range from 2g–12g per tonne of complete feed. Aquaculture feeds are supplied with substantially higher levels of 20g–60g per tonne of feed. In general, riboflavin requirements are positively correlated with the growth rate of animals.

Although feeding stuffs contain some vitamin B_2, nutritionists do not rely on it as a sole source. Monogastric animal feeds are therefore all supplemented with the essential vitamin. The stability of riboflavin throughout feed processing is fairly good. However, considerable loss can occur upon exposure to sunlight.

. . . forms and formulations

Most vitamin B_2 is sold as an 80% product to the feed industry. The diluted vitamin has several advantages over the pure form, it is easier to mix, less dusty, has less electrostatic effects and better flow.

Vitamin B_2 cannot be used for liquid preparations as it is practically insoluble. The alternative product form with some low water solubility is riboflavin 5-phosphate sodium.

. . . market

Prices have eroded dramatically since the early 1990s. In 1999, prices as low as DM 28.00 per kg of 80% vitamin B_2 were recorded in the market. In the first quarter of 2000 prices started to recover slowly.

Table 2.15: Price development of vitamin B_2, 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
DM/kg	36.50	51.60	63.60	65.10	70.70	81.70	85.80

*Note: * First quarter*

Manufacturers from China and India have forced drastic reductions on the world market despite the limited number of usage application. The product is currently offered from Asia in the range of $80–$90 per kg while Roche offer a price of about $200.

60% of global riboflavin production is purchased and consumed by the feed industry. Sales volume for riboflavin in the feed sector was estimated at around 1,980 tonnes in 1999.

. . . companies

Table 2.16 shows the market share of vitamin B_2 manufacturers.

Table 2.16: Market share of vitamin B_2 manufacturers, 1999

Global Market	1980 tonnes
Manufacturer	**% market share**
Roche	49
BASF	25
Takeda	12
Chinese companies	8
Others	6

2.1.1.8 Vitamin B_6

Vitamin B_6 is essential for the

- Metabolism of fats and amino acids
- Formation of haemoglobin
- Normal nerve function

After a phosphorylation reaction, pyridoxine is converted into the coenzyme pyridoxal phosphate. As a coenzyme factor, vitamin B_6 is involved in transamination, decarboxylation, dehydration and desulfhydration, which are all important metabolic processes of amino acids.

Intolerance problems in feeding vitamin B_6 are generally considered to be low. Although it is generally believed that excessive doses are rapidly excreted without doing any harm to the animals, nutritional studies have demonstrated that high doses can cause depressive effects on animal production.

. . . source

Vitamin B_6 occurs naturally in three different forms in plants as the predominant form pyridoxine and in animals as pyridoxamine and pyridoxal. All three forms can be inter-converted and are therefore equal in vitamin activity.

. . . forms and formulations

Commercial vitamin B_6 is almost exclusively offered in the pyridoxine hydrochloride form. Granulated product formulations mix more easily than the fine crystalline powder form.

Supplementation levels in feed range from 1g–5g per tonne of complete feed. Due to the faster growth rate of most aquaculture species, levels in feed can be several times higher.

. . . market

The price level of vitamin B_6 has been fairly stable over the last five years. On average $22.00 and DM 37.60 were paid per kg of product in 1999. In the early 1990s, the price was twice as high.

Table 2.17: Price development of vitamin B_6, 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
DM/kg	36.00	37.60	38.00	38.80	35.60	48.00	76.00

*Note: * First quarter price*

. . . companies

Roche, the main supplier of vitamin B_6, sells only 60% of its present production capacity and other manufacturers are also selling quantities below their capacity. The feed industry alone had an estimated annual demand of 985 tonnes of vitamin B_6 in 1999 (see Table 2.18) and 60% of all produced vitamin B6 is consumed by other industry segments.

Table 2.18: Market share of vitamin B6 manufacturers, 1999

Global Market	985 tonnes
Manufacturer	**% market share**
Roche	52
Takeda	26
Daiichi	18
Chinese	4

2.1.1.9 Vitamin B_{12}

Vitamin B_{12} is essential for:

- Metabolism of nucleotides, proteins, fats and carbohydrates
- Formation of red blood cells

- Healthy nervous systems

. . . source

Vitamin B_{12} is found only in microbial organisms and in animal products.

. . . application

It is an essential vitamin. Therefore, supplementation is required for all types of feeds except that intended for ruminants. In regions where the cobalt content of soil is low, a supplementation of ruminant feed with cobalt or vitamin B_{12} is advised.

. . . forms and formulations

The term vitamin B_{12} (cobalamin) is taken as a generic name for a group of molecules with cobalamin activity. The commercially common form of vitamin B_{12} is cyanocobalamin. Here, the cyano group is bound to the centrally located cobalt atom within the complex molecule of cobalamin. Although cyanocobalamin cannot be found in nature, it exhibits full biological activity. Methyl, hydroxy, nitrite, chloride or other groups can replace the cyanid group without loss of therapeutic effect of vitamin B_{12}.

Even within the group of micro-nutrients, the amount of vitamin B_{12} required is minute. Typical rates of addition to feeds are in the range of 10–40mg per tonne of feed. The high potency of the vitamin creates problems in assuring an even distribution in the compound feed. For this reason it is common practice to apply diluted products in the feed production process.

Generally, there are products with 1.0% and 0.1% vitamin B_{12} concentrations available on the market. Both are fine powder product forms showing a pinkish colour.

. . . market

The price level of vitamin B_{12} has not changed much over the past few years. Aventis (ex-Rhône-Poulenc), being the dominant manufacturer, has supply contracts with the main companies in the vitamin business. Although companies like Roche have developed their own synthesis, the supply contracts from Aventis seem to be favourable enough to keep newcomers out of production.

Given the current state of the market, it is not surprising that the price of vitamin B_{12} has not changed much over the past few years (see Table 2.19). Products from China and India are now penetrating the global market but since the production capacities of the Asian competitors are limited, this has had little effect on Aventis' market share.

For the 0.1% feed grade product, price levels of \$6.60 were seen on the market in the beginning of the year 2000. The strengthening of the dollar against the Euro in the year 2000 has resulted in a constant weakening of the dollar value of the vitamin. In contrast, prices based on the German mark were relatively stable. Taking the pure pharmaceutical grade of vitamin B_{12} as the benchmark price, Asian material came down in price from above \$6,000 to below \$4,800 within the first half of 2000.

Table 2.19: Price development of vitamin B_{12} (0.1%), 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
DM/kg	9.00	9.10	11.80	10.60	10.20	10.40	6.50

*Note: * First quarter*

. . . companies

Aventis has long been the dominant supplier of vitamin B_{12} (see Table 2.20). It is the only vitamin B_{12} manufacturer that has introduced genetically modified organism (GMO) microbes to their fermentation process. This enabled the company to improve the fermentation yield by a factor of 100. All other suppliers rely on the use of traditional GMO-free microbes.The number two company in production is NCPC from China, which sources itsvitamin B_{12} from two plants. The Indian Wockhardt group ranks third in cyanocobalamin production, in 1999 it acquired the ex-Merck Sharp & Dohme subsidiary Merind Limited.

The annual requirement of the feed industry was estimated at approximately 9,200kg in 1999.

Table 2.20: Market share of vitamin B_{12} (1.0%) manufacturers, 1999

Global Market	9,200 tonnes
Manufacturer	**% maket share**
Aventis	69
NCPC	20
Wockhardt	7
Others	4

2.1.1.10 Folic acid

Folic acid (or folate), is essential for

- Regulation of cell growth
- Function of nervous system
- Maintaining normal amounts of red blood cells and haemoglobin

Folic acid is a generic term to describe a number of related compounds that show biological activity of this essential vitamin. Monopteroylglutamic acid is the chemical name of pure folic acid. It is composed of p-aminobenzoic acid, glutamic acid and a pteridine nucleus.

. . . source

Folic acid compounds are found in feeding stuffs of plant and animal origin. Particularly rich sources are yeast, fish meal and extracted soybean meal. Much of the vitamin is present in the feeding stuff in conjugated form. The bound form can be well utilised – unlike biotin. In addition, intestinal microbes help meet the requirement of the host animal through their *in-vivo* synthesis.

. . . application

Deficiency symptoms have been reported in most farmed animals, including fish and shrimp and supplementation of the vitamin is recommended for all monogastric animals. Practical feeds rarely lack adequate amounts of folic acid. Deficiency symptoms may occur in the presence of sulpha drugs. Sulphonamides act as antagonists to folic acid, inhibiting microbial growth in the intestine.

. . . forms and formulations

Usual recommended levels for folic acid range from 0.5mg–2mg per kg of feed. In salmonid fish and shrimp feed these levels are 2–5 times higher. Ruminating animals can obtain their entire requirement by the natural folic acid in feed and by the synthesis of rumen microbes.

Commercial products for premixes and compound feeds are offered as pure substance with 95% activity. Roche offers a spray-dried 80% activity product form.

. . . market

Approximately 80% of all folic acid produced is sold in the feed industry. The pharmaceutical industry consumes about 17%. In 1999, the global feed sector consumed approximately 320 tonnes.

Table 2.21: Price development of folic acid, 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
DM/kg	60.00	69.50	95.00	102	130	178	184

*Note: * First quarter price*

In the early 1990s, folic acid feeding in breeder pigs became popular with nutritional scientists and feed formulators. Subsequently, folic acid consumption grew on average above 5% per annum throughout the following years.

The future development of the supply market is difficult to predict. The demand for folic acid is anticipated to grow at 2% only. Manufacturers have built up over-capacity that will hinder strong price increases in the future. At best, prices will approximate DM 100.00 again. Prices of up to DM 200.00, as they were seen in the late 1980s, will not be reached any more (see Table 2.21).

. . . companies

The global folic acid demand of 320 tonnes is covered by a few reputed companies only. Roche, Takeda and Kongo supply approximately 77% of the global folic acid requirement. Chinese and Indian companies supply the rest (see Table 2.22).

Table 2.22: Market share of folic acid manufacturers, 1999

Global Market	320 tonnes
Manufacturer	**% market share**
Roche	42
Takeda	26
Kongo Chemicals	9
Chinese	17
India	6

2.1.1.11 Biotin

Biotin is essential for:

- Metabolism of amino acids, fats and carbohydrates
- Interconversion of major nutrients
- Formation of healthy skin and hair

In the 1970s, disease symptoms, first shown in chicken and later in pigs, were related to biotin deficiency. Addition of this essential vitamin cured specific conditions like loss of hair, dermatitis and ulceration of the skin. Poultry and swine with skin disorders and birds with Fatty Liver and Kidney Syndrome respond positively to the addition of biotin to the feed. Damage to the foot pads in birds, hoof sole cracks in pigs and hoof damage in cattle can all be cured with the help of biotin. Further general symptoms like growth reduction, impaired feed conversion and fertility disorders are commonly seen in biotin deficient animals.

. . . source

Biotin activity is found in most feeding stuffs of animal and plant origin. It is also synthesised by the microflora in the digestive gut and was long considered not to be required as an additive in compound feed.

Biotin is widely found in feeding stuffs of plant and animal origin. Most cereals, maize and tapioca are poor sources of biotin. In many raw materials biotin is organically bound and so is poorly absorbed from the digestive tract. Availability in most cereals as determined by microbiological assays ranges from 0%–50% availability in maize and soybean meal is close to 100%. In Europe where many feed formulations are based on cereals and tapioca, biotin supplementation rates are generally higher than in the US where the feed is mainly based on maize and soybean meal.

. . . application

It is common practice today to supplement all feeds for monogastric animals with biotin, including fish and shrimp diets. Biotin is currently the second most expensive vitamin after vitamin B_{12}. Usual inclusion rates in complete feed range from 50mg–300mg per tonne of feed. Higher levels are applied to aquaculture feeds and are used for temporary applications, for example to cure hoof horn problems in cattle and horses. The commercial form of biotin is generally offered in a 2% concentration. A 1% form is also available.

. . . forms and formulations

There are two distinct product formulations available. Spray-dried forms provide a product in which each particle is a carrier of biotin activity. The second formulation, often referred to as triturates, is a simple physical blending of 98% diluent with 2% of active vitamin. Since the vitamin concentration in the final feed is extremely low, spray-dried products guarantee the best distribution of biotin. To illustrate the scale of the distribution problem, in order to achieve a 0.1ppm concentration of biotin, 0.1g of the nutrient must be evenly distributed in 1,000kg of compound feed so that each small portion of feed contains an aliquot of the vitamin.

. . . market

Approximately 85% of all biotin produced is consumed by the feed industry. Prices were intentionally driven down by the market leader Roche aiming to regain lost market share and strenthen the market. Annual average prices for the 2% feed grade formulation fell from DM 141.00 per kg in 1990 to DM 45.00 per kg in 2000. At the turn of the year 1999–2000, prices were as low as DM 30.00 per kg. An unexpected product shortage occurred in the second and third quarter of 2000, resulting in a lift up of prices up to DM 105.00 per kg (see Table 2.23).

Table 2.23: Price development of biotin feed grade (2%), 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
DM/kg	45.00	60.50	63.00	67.00	88.00	123	141

*Note: *First quarter price*

The global market in pure biotin is around 32,000 kg. The market is set to grow by 2%–3% per annum. In terms of price the whole market is in turmoil.

. . . companies

After the price collapse, Merck decided to cease production of biotin by the end of 2000. Roche is investing DM 45 million in its new plant in Grenzach, Germany and launched a new production process in October 2000 which it claims will reduce production costs by 60%. The new process and production plant will re-establish Roche as the most cost competitive manufacturer of biotin (see Table 2.24).

Swiss company Lonza terminated their production of biotin in 1997. E-Sung, is rumoured to be evaluating the possible discontinuation of their production. The Japanese companies Sumitomo and Tanabe are the only other biotin producers. Tanabe supplies Aventis. Merck used to supply the other vitamin giant BASF with feed grade biotin but has ceased production. There are currently no Chinese companies in the biotin business.

Table 2.24: Market share of biotin (pure) manufacturers, 1999

Global Market	32,000 kg
Manufacturer	**% market share**
Roche	44
Merck	22
Sumitomo	21
Tanabe	12
E-Sung	1

2.1.1.12 Pantothenic acid

Pantothenic acid is essential for the

- Maintenance of healthy skin and hair coat
- Metabolism of proteins, fats and carbohydrates

Pantothenic acid was one of the last water-soluble vitamins of the B group to be discovered. As a constituent of coenzyme A it occupies a central position in the intermediary metabolism of protein, carbohydrates and fats.

. . . application

Like the other vitamins of the B group, pantothenic acid cannot be stored in quantitatively relevant amounts. Regular supplementation of all monogastric animals throughout the life cycle is therefore recommended.

. . . forms and formulations

The name of the vitamin is derived from the Greek *pantothen*, which means from everywhere. This is apt as pantothenate is ubiquitous in most feed stuff. The commercial form for the animal feed industry is the calcium salt of the vitamin.

In feed formulation it is commonly added in the range of 6–20mg per kg of feed. Turkeys and aquaculture species tend to have a higher requirement. Ruminating animals like cattle, sheep and goats can obtain their requirement through microbial synthesis in the rumen.

Almost 80% of all pantothenate produced is added to compound feed. It is commercially available as d-Ca-pantothenate (d-calpan) and as dl-Ca-pantothenate. The d-form of calpan carries 92% of biologically active pantothenic acid. The racemic mixture of both, the d-form and l-form, is equivalent to only 46% activity. The dl-Ca-pantothenate is produced in Eastern European countries and in China. In terms of market share this product type is playing only a minor role, despite being half the price per kg of product.

. . . market

Annual average prices for d-calpan have risen from DM 26.60 in 1990 to above DM 42.00 since 1996. Throughout the last three years prices have stabilised above DM 40 per kg (see Table 2.25).

Table 2.25: Price development of calcium-pantothenate, 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
DM/kg	43.00	42.90	42.80	42.60	35.00	38.00	26.60

*Note: * First quarter price*

The global market for Ca-pantothenate is approximately 4,700 tonnes. The annual world wide demand for the vitamin is growing at 1%.

... companies

The two vitamin giants, Roche and BASF, cover more than 50% of the global market. In recent years, Chinese companies were able to gain a market share of 14% (see Table 2.26).

Table 2.26: Market share of calcium- pantothenate manufacturers, 1999

Global Market	4700 tonnes
Manufacturer	**% market share**
Roche	32
BASF	20
Daiichi	17
Alps	9
Others	22

2.1.1.13 Niacin

Definition: Niacin is essential for:

- Cell respiration
- Regular function of nerves and digestive system

Niacin is the trivial name for nicotinic acid and nicotinamide. Chemically defined, niacin is a pyridine 3-carboxylic acid. Derivatives that exhibit nicotinic acid activity are all referred to as niacin. Nicotinic acid and nicotinamide posses the same vitamin activity. After its absorption from the intestinal tract, both vitamers are used for the formation of two important coenzymes. They are nicotinamide adenine dinucleotide (NAD) and its phosphorylated form (NADP). Both coenzymes are required in all organs and tissue. They fulfil a central function in the transfer of hydrogen and are especially important in metabolic reactions that provide energy to the animal.

Niacin is widely found in feeding stuff of animal and plant origin. Some of the niacin activity is present in a bound form, which reduces the biological availability of the vitamin for animals.

In ruminating animals, niacin supplementation showed several beneficial effects. Milk production and milk composition could be improved in dairy cattle. Incidence of ketosis, a metabolic disease, is reduced in postpartum cows. Both indications may be linked to each

other, since many postpartum cows go through some borderline ketosis, which has a direct impact on the milk yield. The effects are most pronounced in energy-rich diets with a low crude fibre concentration. Under such feeding conditions beef cattle do also respond on niacin supplementation by better feed conversion and less metabolic problems.

. . . application

In common with the other vitamins of the B group, dietary niacin is required by all monogastric animals but unusually, animals are capable of synthesising nicotinic acid, from the amino acid tryptophan. It is therefore difficult to establish an exact requirement for this particular vitamin. Since niacin is relatively cheap in comparison to tryptophan it is generally added to feed. Trytophan is reserved to complement the amino acid composition of the diet which is its more vital purpose

. . . forms and formulations

The levels of addition recommended by the industry are 3g–12g per head and day for dairy cattle around time of parturition. For beef cattle on concentrated feed recommended levels are 1g–4g per head and day.

Supplementation levels for monogastric animals are in the range of 20–80mg/kg (ppm) of feed. Fish and shrimp feeds as well as starter and breeder bird feeds may be supplemented with 100mg and more per kg of feed.

. . . market

Niacin price changes showed only little fluctuation over the past 10 years. One reason is that the vitamin is traded more as a chemical commodity than as a fine chemical speciality. The annual average price for niacin has declined by 10–20% throughout the last 5 years (see Table 2.27).

Table 2.27: Price development of niacin, 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
DM/kg	8.00	7.90	9.40	8.50	8.30	10.70	9.90

*Note: * First quarter price*

The global market for niacin is split into two different commercial products, nicotinic acid and nicotinamide. As they are interchangeable, they can be regarded as one product. The total market for niacin is just over 19,000 tonnes.

. . . companies

On the manufacturing side there are three companies, which dominate the market (see Table 2.28). Lonza the market leader, sells the majority of its niacin through the company Roche that markets the product under its own brand name Rovimix Niacin. Several Indian companies are involved in niacin production, namely IDPL, Rupal, Veerchemi, Khoj Chemicals and Alpha Chemicals. Its total output, however, barely reaches 1,000 tonnes per annum. Products are mostly consumed within the Indian subcontinent.

Table 2.28: Market share of niacin manufacturers, 1999

Global Market	19,000 tonnes
Manufacturer	**% market share**
Lonza	53
Degussa/Vitachem*	28
Nepera	16
Others	3

*Note: * Vitachem is a joint venture company of Degussa and Reilly*

2.1.1.14 Vitamin C

Vitamin C is essential for:

- Growth and repair of cell tissues
- Formation of gums, bones, skin and connective tissue
- Resistence to disease

. . . application

Vitamin C is a water-soluble vitamin. Poultry, swine and other farm animals have the ability to biosynthesise vitamin C in the liver or in the kidneys. Nevertheless, they may develop marginal deficiencies after exposure to external stress factors or diseases. Supplementation of the vitamin to feed is suggested to overcome such nutritionally deficient episodes. Although these animals are basically self-sufficient with regard to vitamin C, situations can occur which can either limit their ability to biosynthesise the nutrient, or the physiologically required amount can exceed the actual synthesis of vitamin C.

In domestic fowl the ability to synthesise vitamin C develops during the first stages of life after hatching. Prolonged exposure to stress factors, such as adverse climate or prolonged disturbance, can cause temporary deficiency as can dysfuntions of the liver or kidney caused by infections or mycotoxins. In such cases the addition of vitamin C to feed can help overcome the deficiency.

Fish and some crustacean species are dependent on a regular external supply, so for these aquacultured animals the vitamin is an essential nutrient.

Most studies on vitamin C requirements have been conducted with ascorbic acid in its non-protected form, but these do not take account of the lability of vitamin C. In its unprotected form vitamin C is easily and irreversibly oxidised to the 2,3 diketogulonic acid form. As the oxidised form has lost its nutritional function it is therefore impossible to achieve a meaningful estimate of true dietary requirement.

. . . forms and formulations

The feed additive industry offers a wide range of vitamin C formulations for the production of compound feed and nutritional/veterinary supplements. These are:

- Vitamin C – straight acid form
- Vitamin C salts – Na, Ca, Mg salts

- Voated vitamin C crystals – coatings: ethyl cellulose, silicone, fat
- Vitamin C beadlets – vitamin crystals embedded in organic matrixes
- Vitamin C esters – ascorbyl-palmitate, ascorbyl-phosphate, ascorbyl-sulphate

The straight vitamin C is the product of choice in liquid preparations for immediate or emergency nutritional use. The Na-salt of vitamin C is mainly used in water-soluble powders. The instability of vitamin C has been a major problem in compound feed production since the early 1960s. The vitamin industry has developed various coated forms, all of which show incomplete coverage of the vitamin C crystals. None of them provide sufficient protection against adverse physical factors, such as heat, pressure, humidity and oxygen. This is particularly the case during the pelleting and extrusion processes of feed production. The most stable form of vitamin C in compound feed is found with the sulphate and phosphate-esters of ascorbic acid.

The feed additive market offers ascorbyl-phosphate forms with varying purity. All product forms have demonstrated excellent availability to the animal organism. The sulphate-form of ascorbic acid generally has availability of only 2–5% and has been shown to be closer to 0% in primates and guinea pigs.

The phosphate form of ascorbic acid has been widely accepted in the feed industry and is used whenever a stable and nutritionally available vitamin C form is required.

... market

Vitamin C prices have gone through dramatic changes since 1996 when Roche initiated a steady decrease in price. The market leader was motivated to bring down the price to defend its global market position against competitors from China and India. In 1996, more than 40 different factories were involved in the production of vitamin C. The increasing number of companies had been attracted by growing product demand combined with beneficial profit margins. At the time of the price collapse, construction was due to begin on more large-scale plants.

Prices dropped from DM 23.50 in 1995 to DM 13.80 in 1996. The next few years brought prices down further. Although average market prices, as given in Table 2.29 are higher, prices below DM 9.00 per kg in 1999 and $4.00 in mid 2000 have been recorded.

Table 2.29: Price development of vitamin C, 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
DM/kg	11.20	11.00	10.80	11.20	15.80	23.50	20.60

*Note: * First quarter*

The benchmark for the vitamin C products is the straight crystalline vitamin C. Approximately 33% of all vitamin C consumed by the feed industry is in the phosphorylated form, which is approximately four times more expensive.

... companies

The majority of all vitamin C produced is consumed by the human food and pharmaceutical market. The market leader is the Swiss company Roche. With its production plants in Scotland and in the US it produces approximately 40% of all vitamin C consumed. In 1999 there were only 3 manufacturing companies left in China. In India there are no longer any operational plants. Merck, which had entered into a joint venture vitamin C production project with BASF and Cerestar of the Netherlands in 1999, were expected to give up the loss making business by year-end 2000. Losses written off this year in vitamin C production are reported at €30 million.

The feed market is estimated at about 6,200 tonnes per annum. This equals approximately 8% of the total consumption by industry sectors. With its strong position in the feed market for stable vitamin C forms, Roche reached a 55% market share globally. The turnover in 1999 was estimated at DM 151 million (see Table 2.30).

Table 2.30: Market share of vitamin C manufacturers, 1999

Global Market	6,2000 tonnes
Manufacturer	**% market share**
Roche	55
China	21
BASF	13
Takeda	10
Other	1

2.1.1.15 Summary of the global vitamin market

The global vitamin market has undergone some dynamic growth over the past five decades. While in the late 1960s and early 1970s the volume growth was above 10% per annum, growth rates came down to 5% till the late 1980s. The 1990 market size was worth approximately DM 1700 million. At actual exchange rate, this figure corresponds to €870 million. In 1995, the sales turnover had grown to a value of €1,190. The average 7% increase per year was achieved by significant price increases and some moderate expansion of vitamin use.

Between 1995 and 1999 the sales value fell by €16 million. The strength of the German Mark against the dollar was overshadowed by the erosion of previously high prices after 1996. Volume growth of vitamins is estimated to average close to 0% for the five year period since 1996. Growth was mainly hampered by the economic crises in Asia and in Latin America.

During the next five years, the Asia-Pacific region is projected to be the fastest growing market for vitamin use, in terms of volume. This region will increase its position in global consumption of vitamins from 17% in 1999 to 22% in 2004. Europe and the Americas with their slowly growing poultry and pig markets are expected to lose market share, despite slightly higher vitamin consumption.

Table 2.31: Global and regional development of vitamin consumption, 1990–2004

	1990	1995	1999	2004
Global Market € million*	870	1190	1174	1408
% Market share by region				
Europe	42	40	36	34
North America	34	31	32	29
Latin America	10	11	11	12
Asia-Pacific	10	15	17	22
RoW	4	3	4	3

*Note: * All sales value figures are expressed in Euro currency*

The sales turnover was around €870 million in 1990. Five years later sales reached €1,190 million. The strong increase in sales number was mainly driven by the successful price fixing strategy of the major vitamin manufacturers. With the break-up of the international cartel in 1998 some individual vitamin prices started to fall. Other vitamin prices had already been reduced in 1996 and 1997 to combat aggressive pricing from Chinese companies.

Sales turnover of vitamins are anticipated to grow at 3% per annum till 2004. Volume increase is estimated at 2% and price increases will be responsible for the additional 1%. Recoveries of sales prices are expected for vitamins E, C, biotin and vitamin B_2.

2.1.2 Amino acids

Amino acids are structural components of proteins. The basic chemistry of amino acids is composed of two functional groups. These are an amino group (NH_2) and an alpha carbon atom of a carboxyl group (COOH), which are both linked with each other. All amino acids found in plant and animal proteins are l-stereo isomers. Most amino acids found in animal proteins belong to one of 20 different amino acids. All of them are physiologically essential. Depending on the combination of the 20 nutrients, they can form a multitude of proteins, which all have different but characteristic properties. Amino acids can be subdivided by their chemical structure (polar or non-polar, acid or basic) or by the animal's ability for own synthesis.

Amino acids that cannot be synthesised by the animal organism are defined as essential. Amino acids are mostly supplemented through feeding stuffs, which contain proteins. Each type of protein is composed of a particular set of essential amino acids. In case of insufficient supply of a particular nutrient, the addition of pure amino acid can complement the feed to form a complete diet regarding amino acids.

There are only a few pure amino acids commercially available for feed formulations. These amino acids are the most limiting ones in compound feeds. The rational for use is in

- Optimising feed formulations
- Reducing production cost for animal production
- Minimising excretion of nitrogen.

The commercial availability of amino acids at low cost provides the feed formulation manager with the opportunity to complement compound feed with amino acids which, in case

of marginal content, would limit the animals' performance. This may result in relevant benefits over cost. Lysine, for example, is widely supplemented wherever maize and grains are the major ingredients in complete feeds.

Other benefits of commercial use of pure amino acids are given by the lower protein concentrations required in feed. This may result in savings of protein resources for other nutritional purposes. Further, the nutrients can replace excessive protein in feeds resulting in more efficient utilisation of nitrogenous nutrients and energy. And finally, lower protein content in the feed leads to less nitrogen excretion, thus reducing environmental pollution.

2.1.2.1 Lysine

Lysine is an essential amino acid. In the formation of collagen and digestive enzymes it plays an important constituent part. Lysine is not involved in reversible transamination reactions.

. . . source

Cereal grains and maize are low in lysine. Animal proteins, on the contrary, are generally rich in lysine. Simple feed compositions without lysine-rich ingredients favour the use of the pure feed additive. The practical consequences of the BSE cases in Europe discouraged the use of lysine-rich rendering meal. Wide use of Least Cost Formulation (LCF) programmes and low pricing level of lysine have further boosted sales turnover of lysine.

. . . forms and formulations

Lysine is produced by fermentation process. The resulting commercial product is in the form of the l-lysine isomer. In animal nutrition l-lysine shows high bioavailability. D-lysine, on the contrary, cannot be utilised by animals.

Typical commercial product formulations are dry and liquid l-lysine HCl (mono-hydrochloride) and straight l-lysine. Sulphate and phosphate derivatives of the amino acid are also available. Depending on the type of product, lysine concentrations vary between 22% and 78%.

. . . market

Prices for l-lysine are characterised by high volatility, within individual years and also over longer periods of time. As recently as 1999 prices as low as DM 1.80 or $0.80 were offered to the market. In he first quarter of 2000 prices stabilised again around DM 3.30 and $1.80 (variation: 1.50–2.45) per kg of product. Low price levels in 1994 and 1995 were mainly caused by the ADM entering the market.

Table 2.32: Price development of l-lysine (l-lysine HCl), 1995–2000

Year	2000*	1999	1998	1997	1996	1995
DM/kg	3.30	2.50	4.10	6.50	4.20	3.50

*Note: * First quarter*

. . . companies

In 1999, the feed industry had an estimated annual requirement of 430 tonnes. ADM and Ajinomoto are the main suppliers to the market followed by BASF, Kyowa Hakko and Cheil Jedang (see Table 2.33). Degussa has formed a joint-venture project with Cargill USA and they will soon enter the market with substantial amount of l-lysine. A few smaller production plants are located in China and one in South Africa. It is worth noting that there is a production overcapacity in the range of 40%, which will not allow for major price increases in future.

Table 2.33: Market share of lysine manufacturers, 1999

Global Market	430,000 tonnes
Manufacturer	**% market share**
ADM	28
Ajinomoto	26
BASF	15
Kyowa Hakko	13
Cheil Jedang	10
Others	5

The annual growth rate for lysine is estimated at 5% for the next five years.

2.1.2.2 Methionine

Methionine is a sulphur-containing essential amino acid. It acts as a building block in the formation of proteins. Additionally, it has a donor function in the transfer of methyl groups. After de-methylation reactions it can be recycled to methionine. Further down its metabolisation, methionine is a precursor for the amino acids cysteine and cystine.

. . . source

Methionine is found in high concentrations in animal proteins; meat, bone meal and fishmeal are all rich sources. Soybean meal is also a good source. Methionine concentration is low in grains and maize.

. . . forms and formulations

Industrial sources of methionine are available in the form of dl-methionine.

Synthetic methionine is a mixture of almost equal amounts of both isomers. Although the d-form is not found in nature, it can be efficiently utilised by animals. This ability to utilise both forms does not apply to other amino acids like lysine and threonine.

Another commercial product that can fulfil methionine requirement is the hydroxy-analogue of dl-methionine. Animals have an indispensable requirement for the preformed carbon body of the amino acid. Whereas the amino nitrogen can be added to the carbon skeleton by metabolism, the skeleton itself cannot be biosynthesised. There is an ongoing debate about the biological efficacy of the methionine hydroxy-analogue (MHA) in relation to dl-

methionine. It is commonly accepted that dl-methionine has a higher activity on an equimolar basis and, even more so, on a weight-to-weight basis.

Dry dl-methionine is offered as a product with minimum 98% purity. The concentration of the liquid form is 40%. A protected, so-called rumen bypass dl-methionine, has been marketed for ruminants though its commercial success in terms of sales quantity has been modest.

. . . market

Average annual methionine prices between 1995 and 1999 varied by about 25% (see Table 2.34). Price levels are mainly determined by the cost and availability of protein-rich feeding stuffs and the availability of methionine.. In the first quarter of 2000 prices varied between \$2.40 per kg and \$3.40 per kg. MHA costs were \$0.40–\$0.50 less per kg.

Table 2.34: Price development of dl-methionine, 1995–2000

Year	2000*	1999	1998	1997	1996	1995
DM/kg	5.50	4.70	5.70	6.30	5.10	4.80

*Note: * First quarter*

. . . companies

In 1999, the annual methionine requirement of the feed industry was estimated at 440,000 tonnes. Degussa is the No 1 supplier for dl-methionine, followed by Aventis and Mitsui. Mitsui is the major supplier for MHA and markets and sells MHA through its company Novus, which is based in the US (see Table 2.35). Mitsui also holds a 70% stake in the dl-methionine producer Nippon Soda.

Table 2.35: Market share of dl-methionine manufacturers, 1999

Global market	440,000 tonnes
Manufacturer	**% market share**
Mitsui/Novus*	34
Degussa	30
Aventis*	28
Others	8

*Note: * MHA and DL-methionine*

Novus and Degussa have both announced ambitious expansion projects of their production plants. The present production capacities are already exceeding the demand of the feed industry by around 30–40%. Demand for methionine is projected to grow at an average annual rate of 5% until 2004.

2.1.2.3 Threonine

Threonine is an essential amino acid that is part of various important protein as they are found in digestive enzymes and immunoglobulins. Unlike other amino acids, it cannot

participate in transamination reactions. It is closely related to the formation of glycine, acetyl-CoA and pyruvate. Vitamin B_6 is involved in the dehydration process of the threonine breakdown process.

. . . source

The amino acid is found at high concentrations in animal proteins and soybean meal but only small amounts can be detected in grains and maize. In most practical feeds it is not a limiting nutritional factor. Therefore, the commercial form of threonine is not yet widely used in feed formulations.

The first commercial products appeared in the early 1990s. Threonine is produced by a fermentation process. Pure threonine is offered with a minimum concentration of 98%.

. . . market

At the beginning of 2000, prices fluctuated around DM 7.20 ($3.10–$4.40) per kg of product. There was some price recovery at the beginning of 2000 against 1999, but prices weakened again in the second and third quarter. Larger quantities are being offered below DM 7.00 per kg. Price development from 1995–2000 is shown in Table 2.36.

Table 2.36: Price development of threonine, 1995–2000

Year	2000*	1999	1998	1997	1996	1995
DM/kg	7.20	5.90	8.10	8.30	6.80	4.70

*Note: * First quarter*

The worldwide demand for threonine was estimated at 15,000 tonnes for the year 1999 but production capacity is at least 50% higher.

Annual growth potential is difficult to forecast but a two-digit annual growth potential is likely, provided prices come down further. Bacterial strain improvements will increase yield and help to reduce production costs. Considering the overcapacity of the industry, competitive pressure is anticipated to persist. Average annual percentage growth of threonine use is conservatively estimated at 10%.

. . . companies

Table 2.37: Market share of threonine manufacturers, 1999

Global market	15,000 tonnes
Manufacturer	**% market share**
Ajinomoto	51
Degussa	29
ADM	17
Others	3

2.1.2.4 Tryptophan

The essential amino acid tryptophan is another building block of complex proteins. It is not present in collagenous protein, through its catabolic pathway tryptophan can be transferred to a provitamin form of nicotinic acid. Other important metabolites of tryptophan catabolism are the hormones serotonine, melatonine and tryptamine.

. . . source

Most protein-rich feeding stuffs of plant origin contain high concentrations of tryptophan. Relatively low concentrations are found in maize, grain and meat meal. In practical diets the pure amino acid is not currently widely used.

The commercial product is produced by fermentation.

. . . forms and formulations

The product on sale contains a minimum of 98% of l-tryptophan. It must be stored away from direct light and it is also sensitive to oxidation processes and low pH.

. . . market

The pricing level of tryptophan has deteriorated since 1997 (see Table 2.38). Further lowering of product price should increase inclusion in feed formulation. Product use may therefore increase. In the third quarter of the year 2000 tryptophan prices were still on a downward slide. Prices below $25.00 and DM 50.00 per kg have been recorded.

Table 2.38: Price development of tryptophan, 1997–2000

Year	2000*	1999	1998	1997
DM/kg	65.00	82.00	108.00	105.00

*Note: *First quartere*

The global consumption of tryptophan is still at an early stage. Annual volume sales are estimated at 750 tonnes for 1999. Sales turnover accounts for approximately DM 62 million.

. . . companies

More than 40% of the market is supplied by ADM (see Table 2.39).

Table 2.39: Market share of tryptophan manufacturers,1999

Global market	750 tonnes
Manufacturer	**% market share**
ADM	43
Ajinomoto	23
Mitsui	17
Others	17

Ajinomoto inaugurated a new production plant in August 2000. Production capacity is planned at 1500 tonnes per annum. With the enlarged production capacity it is predicted that the sales price will decline further. This will foster broader use of the essential amino acid in feed formulations. Projected annual growth of the tryptophan market is estimated at over 10% per annum.

2.1.2.5 Taurine

Taurine is a sulphur amino acid, which occurs as free amino acid in all animal tissues. Most mammals can synthesise taurine from the degradation of methionine and cystine. None of the felidae species can synthesise taurine in sufficient quantities to meet their nutritional requirements. Deficiency of this essential nutrient leads to development of typical disease symptoms in cats such as central retinal degeneration, impaired hearing ability and reproductive disorders.

. . . application

Taurine first became popular in the food industry, where it is offered as a nutritional additive, particularly in the so-called designer drink segment. Like caffeine it acts as a stimulant. In feed production, taurine use is by and large restricted to cat food where it is added to complete feed to overcome inadequacy in feeding stuffs. On a dry matter basis taurine supplementation is twice as high in canned food than in expanded food.

The regional demand for taurine is confined to the developed pet food markets. Europe, North America and Japan are the main regions where a developed cat food industry exists.

. . . market

On a global scale, approximately 2,400 tonnes of taurine are consumed in the feed industry. Taurine prices were above $6.00 per kg at the time of product launch. Today, prices are down to $2.00 to $4.00 per kg. Chinese producers offer the lowest prices. As a whole, the market is believed to have a value of $7 million.

2.1.3 Trace elements and organically bound minerals (mineral proteinates)

All living organisms are dependent on the supply of minerals for growth and maintenance. There are around 45 elements that play important roles as constituent materials in body tissue and in metabolism. Unlike other nutrients, minerals can neither be produced nor used up by the organism. Organically bound minerals are formed by bonding amino acids or peptides to trace minerals.

. . . source

Most minerals are sourced from soils and rocks and the technology of production is generally simple. They are usually added to the feed in the form of salts, like oxides, sulphates, chlorines or carbonates. Most minerals are inexpensive and they represent only a small fraction of the overall cost of feed.

. . . forms and formulations

Some companies that specialise in mineral additives offer so-called proteinated minerals. The term is not technically correct, since the minerals are not bound to proteins but amino acids or

peptides. Nevertheless, the term is commonly used. After bonding the minerals to amino acids or peptides, the adduct becomes electrically neutral and pH stable. Organically bound minerals are available for chromium, manganese, iron, cobalt, nickel, copper and zinc, which are all elements of the first transition system of the periodic system.

Several benefits are attributed to the use of organically bound minerals. The most important is related to improved mineral absorption from the digestive tract. Further benefits are claimed, all of which relate to improved mineral availability for better growth yield, enhanced reproduction performance, improved carcass quality, less skeletal disorders and increased immune response.

Selenium in the form of sodium selenite or selenate salt is a highly toxic mineral. Organically bound to methionine or cysteine it can help to reduce the potential of selenium poisoning. Chromium salts are generally not supplemented to feeds. In feeding trials, the bound form of chromium has demonstrated a growth-promoting effect in fattening pigs. Organically bound chromium is thus making some inroads in the pig feed market.

Organically bound minerals have been on the market for several years. They are increasingly accepted as alternative products to mineral salts. In Table 2.40, the nutritional advantages of the most important organically bound minerals against plain mineral salts are listed. It should be noted that many of the claims made are still lacking sound scientific evidence.

Table 2.40: Organically bound mineral products versus inorganic mineral salts

Organically bound mineral (OBM)	Inorganic mineral salt (IMS)	Advantages of OBM versus IMS
Selenium proteinate	Sodium selenite/selenate	Low toxicity, high absorption
Zinc-proteinate	Zinc sulphate/oxide	High absorption, less excretion, less soil load
Copper-proteinate	Copper sulphate	High absorption,less excretion, less soil load
Iron-proteinate	Iron sulphate	High and fast absorption
Chromium-proteinate	Not supplemented	Acts as a growth promoter in pigs
Magnesium-proteinate	Magnesium sulphate/oxide	High absorption, high storage rate

... market

The mineral market is estimated to be worth DM 920 million. Out of this, calcium has a share of 22%, phosphates of 36% and magnesium of 12%. The remainder comprises of all the other trace elements. Volume-wise, the largest source of calcium is crushed limestone, while supplemental phosphorous is sourced from phosphates, phosphoric acid and ammonium orthophosphate. Potassium is added to feeds in the form of chlorine or sulphate. The single largest mineral as far as volume is concerned is sodium chlorine. Prices of such bulk minerals are generally low. Prices throughout the past few years have been on a downward trend and pressure on prices is expected to continue.

Compared with mineral salts, organically bound minerals are high-priced products. They are marketed as products with additional nutritive benefits over mineral salts and are sold in specialised feed with high profit margins, such as horse and pet foods. They are also succesfully marketed where the cost factor of the feed is of lower importance, for example

starter pig and calf feeds. Prominent sales areas are Europe, US, Japan and Korea. In other regions of the world, the high prices are limiting more frequent use applications.

In general, prices for organically bound minerals are oriented downwards (see Table 2.4.1).

Table 2.41: Price development of organically bound minerals, 1995 and 1999

Product	Concentration%	1995, $/kg	1999, $/kg
Selenium	0.1	3.00	1.80
Chromium	0.1	4.00	3.20
Copper	10	4.00	3.20
Cobalt	10	15.00	8.70
Iron	15	4.00	2.90
Magnesium	10	3.00	3.00
Manganese	15	3.00	3.00
Zinc	15	3.00	1.90

The 1% feed grade selenium proteinate was priced in the early 1990s at $9.00 per kg. After its successful introduction to major markets it is now available at prices as low as $3.00 per kg. Similar price decreases are seen for the 0.1% product form and the bound forms of magnesium and iron.

The estimated turnover for organically bound minerals is approximately 20,000 tonnes. This reflects a percentage increase of about 66% within five years. Lower prices have contributed to increasing use on a global basis. A second factor bolstering the demand is related to the increasing environmental concerns in Europe and elsewhere. The use of proteinated minerals is promoted as a means to reduce excretion of trace elements which are potential pollutants of soil and underground water. Several countries in Europe have already reacted to these concerns, particularly in the Benelux, and the Nordic Countries of Europe. The regulatory body of the European Union (EU) has approved several proteinates (eg zinc proteinate). National laws allow the use of all other proteinates.

Table 2.42: Global consumption of organically bound minerals 1995 and 1999

Product	1995, tonnes	1999, tonnes
Selenium	5,000	9,000
Chromium	500	1,000
Copper	800	1,900
Zinc	1,500	2,400
Magnesium	800	1,600
Iron	700	1,000
Others	3,000	3,500
Total	12,300	20,400

In relation to the vast market of minerals, the turnover of mineral proteinates is still small. In sales value it is worth barely 10% of the total mineral market. A growth rate of 5–10% is anticipated for the next five years. Despite the projected fast growth rate for organically bound minerals, their importance will remain low. The dynamic increase in volume sales

between 1995 and 1999 is overshadowed by the strengthening of the dollar against the German Mark ($1 = DM 1.423 versus $1 = DM 1.835. Therefore, the turnover in dollars only increased from 45 million to 51 million.

Despite a projected substantial volume growth for proteinated minerals (see Table 2.43), the sales turnover will increase by only 1% per annum. It is anticipated that price decreases for the specialised minerals will almost balance out the anticipated volume growth.

Table 2.43: Global sales development of organically bound minerals by sales regions, 1995–2004

	1995	1999	2004
Global sales ($ million)	45	51	54
% market share by region			
Europe	33	35	38
US	42	39	37
Asia	19	20	20
RoW	6	6	5

. . . companies

Major manufacturers of proteinated minerals are listed below in alphabetic order. The non-transparent character of this business makes it difficult to arrive at a reasonably estimate of market share figures. Zinpro and JH Biotech are considered to be the market leaders in this segment.

Manufacturers of organic minerals:

- Alltech
- Ashland /Weinstein Incorporated
- JH Biotech
- JHN Corporation
- Kemin
- Lesaffre
- Pryia
- Whilesale Feed Incorporated
- Zinpro

2.1.4 Accessory feed substances

In addition to vitamins and amino acids there are several other compounds that are required in small amounts for the normal functioning of the animal's body. Accessory feed substances are organic compounds with a nutritive character, but that do not match the definitions of vitamins or amino acids. Their use application is often limited to some particular metabolic functions. Since other compounds can replace the nutrients, their essentiality can be disputed.

2.1.4.1 Choline

Choline is often referred to as a vitamin though it does not match the classical definition. It has no cofactor function in enzyme reactions. The addition rate is in multiples of 100g per tonne of feed and it can be synthesised from excessive methionine in the metabolism. Choline is a colourless, viscous liquid with a relatively simple molecule. It is a quaternary ammonium compound and is widely found in nature.

Major physiological functions are:

- Donor of methyl groups
- Inter-conversion with other methyl donors including methionine, folic acid, betaine
- Lipotropic agent
- Structural component of important phospholipids responsible for maintaining cell membranes and transmission of neural impulses

. . . source

Choline is found in all plants and animals. Some literature refers to choline as vitamin B_4, others as vitamin B_7. Neither of these vitamin codes are commonly accepted nor should choline be linked to any vitamin.

. . . forms and formulations

Inclusion rates for choline chloride usually range from 200g–1,500g per tonne of feed. Turkey and fish feed tends to be supplemented at a higher level. Choline chloride is a typical bulk chemical that is produced on large scale. Concentrations of most sales products are 50%, 60% or 70%. Typical carrier materials for the powder products are either silica or vegetable based. Liquid choline chloride is also available.

. . . market

The global market for choline chloride grew from less than 100,000 tonnes in the late 1980s to around 150,000 tonnes in the 1990s (see table 2.44). The bulk chemical has become a standard feed additive. The price has always been low in comparison to the more complicated vitamin molecules. Despite its commodity character, market prices have fallen constantly in recent years. Since prices decreased faster than the sales volume grew, the market value declined.

In 1990 prices for choline chloride were recorded in the range of \$1.50–\$2.00 per kg of activity. In 1999, the feed industry could purchase it at \$1.10–\$1.20 per kg active. The corresponding prices were DM 2.20–DM 2.40.

Choline chloride is a chemical commodity product with small profit margins. Therefore, no major market growth in terms of quantity and turnover is expected. Most market growth is anticipated from Asia. The global market value for choline chloride will remain stable at the current figure of \$160 million.

Table 2.44: Sales development of choline chloride by region, 1995–2004

Year	1995	1999	2004
Sales by region in 1,000 tonnes			
Europe	44	35	39
North America	45	46	42
Latin America	25	30	33
Asia	27	27	35
RoW	5	4	5
Total	146	143	159
Value ($million)	255	161	160

. . . companies

Six companies, all with headquarters in Europe or the US dominate the global production of choline chloride. Market share figures of the companies are recorded in Table 2.45.

Table 2.45: Market share of choline chloride manufacturers, 1999

Manufacturer	% market share
Chinook	19
Ducoa	19
BASF	17
Akzo Nobel	14
UCB	14
ICI	7
Others	10

2.1.4.2 Carnitine

The active isomer of carnitine is the l-form. The d-form is normally removed from the racemate in the production process. It is an essential component in generation of energy from long-chain fatty acids in the mitochondria. No deficiency symptoms are known for carnitine in domestic animals. Therefore references to carnitine as vitamin B_{11} and B_T are not justified and should be avoided.

. . . source

L-carnitine is biosynthesised in the liver and the kidneys from the two essential amino acids l-lysine and l-methionine.

. . . application

Manufacturers of carnitine are promoting the claim that supplementation of the compound will benefit piglets and companion animals. Although carnitine is synthesised in the host animal, some, such as racehorses and racing dogs may not be able to cover their full requirement.

A market for carnitine is developing in the weaner pig industry. Scientific evidence is not clear and further research is required to confirm the claims made by the industry. In horses and pet food formulations, supplementation of carnitine is widely accepted. This feed industry segment has developed a sizeable market for the metabolite.

The manufacturers also promote the addition of carnitine to poultry feed, but despite the marketing this use of carnitine is not well established.

The global market for carnitine in feed application is still small in comparison to the food and pharmaceutical markets. Carnitine usage is one of the booming neutraceuticals, particularly in the beverage industry.

. . . forms and formulations

Typical application rates for carnitine are 25–50mg per kg in pig feed, 20–40mg per kg in poultry feed, 200–500mg per kg in pet food and up to 5g daily per horse. The global market for carnitine in feed is estimated at approximately 180 tonnes. Considering that in 1990 the market was virtually non-existent, it has since grown to a respectable size.

. . . market

At the time of market introduction carnitine was priced as high a SwF 250 per kg activity. With the appearance of Chinese producers in 1996, prices fell considerably. At the beginning of 2000, carnitine was sold at around $12.00–$15.00. European prices were in the range of DM 35–DM 50 per kg of product in 1999.

The market value of carnitine is almost worth DM 7 million. However, despite the growing popularity of carnitine use, particularly in Europe (see Table 2.46), the feed market represents no more than 4% of overall use.

Table 2.46: Global development of carnitine use and sales turnover, 1995–2004

Year	1995	1999	2004
Sales in tonnes by region			
Europe	75	94	125
North America	45	50	65
Asia	25	28	40
RoW	5	8	10
Total	150	180	240
Sales value (DM million)	7.5	6.6	6.5

. . . companies

Lonza, the Swiss chemical company is dominating the carnitine market and 65% of all carnitine consumed in the feed market comes from Lonza (see Table 2.47). Chinese manufacturers are enjoying a growing market share year after year due to aggressive pricing policy. The Italian company Sigma Tau is almost absent in the feed market.

Table 2.47: Market share of l-carnitine manufacturers, 1999

Manufacturer	% market share
Lonza	65
Sigma Tau *	<1
Others	34

*Note: * Sigma Tau has a major market position for food and pharmaceutical grade products, but is almost absent in the feed business*

2.1.4.3 Inositol

Inositol is a natural compound with several biological functions. Inositol is a non-essential nutrient insofar as no deficiency symptoms are known for terrestrial animals. Chemically, inositol is a cyclic hexa-alcohol, which belongs to the group of phospholipids.

. . . source

Nine isomeric forms are known. Myo-inositol is the only biologically active isomer, which occurs in plants and animals in measurable amounts.

The main source for commercial production of inositol is from plant phytic acid. Common plant sources in industrial production for inositol are rice, maize, barley, wheat, soybeans or others. After the process of wet milling of grains and seeds, the nutrient is then separated from the steep water by pH sensitive precipitation. Finally, phytate is hydrolysed through physicochemical or enzymatic processes to myo-inositol and phosphate. Another applied method of production is from the slurry of lysine production and it is claimed that the production costs are lower than the wet milling process.

. . . application

Inositol is a commonly used additive in shrimp diets. The crustaceans have an essential requirement for phospholipids. If phospholipid concentration is marginal in feed, shrimps will react with growth depression. In the feed formulation for finfish, inositol is widely recommended, although fish seems not to have a requirement for preformed phospholipids. In aquaculture diets, inositol can be replaced by other phospholipids without any negative effects.

In chicken nutrition, inositol is known to improve the metabolic disorder fatty liver syndrome. Application in feeding practice, however, is scarce.

. . . forms and formulations

Recommended supplementation levels vary according to aquaculture species from 100g to more than 1,000g per tonne of feed.

. . . market

The global demand for inositol in the feed industry was estimated at 1,550 tonnes for 1999. Most of the production is located in Japan and China. Prices have been fluctuating over the past few years, mainly because of temporary product shortages. In 1999, the global market

value was estimated at $23 million. The volume demand is projected to grow in the range of 5%–10% per annum. At the beginning of 2000 inositol from China was offered at $6.00–$6.50 per kg. Japanese inositol was offered at $14–$18 per kg.

2.1.4.4 Betaine

Betaine is a donor of labile methyl groups, which can spare, but not replace, choline and methionine. Betaine itself can be synthesised from choline. Its major functions are in transmethylation reactions and to serve as a compound to regulate osmotic pressure within the cell.

Betaine is promoted for the following functions in animal nutrition:

- Efficient methyl group donor for methylation processes
- Protective factor against fatty liver and for lean carcass (lipotropic substance)
- Aiding in cell osmoregulation

. . . application

If supplemented at all, betaine is included in feed formulations for swine, poultry and fish. In poultry it is claimed to result in higher breast-meat yield and lower fat content in the whole carcass. Further effects are improved heat tolerance in monogastric animals. In salmonid fish, betaine can improve the osmotic tolerance during period of transfer from fresh water to seawater. There is some evidence that birds with coccidia (a protozoa infection) will show less intestinal lesions when feed is supplemented with betaine. It is believed that the birds cope better with the negative effects of the infection through better maintainance of the water balance under cellular invasion of the coccidia.

Claims about the nutritional benefits of betaine are still the subject of debate within the scientific community. However, it is commonly accepted that betaine cannot replace methionine as a building block in proteins.

. . . forms and formulations

Betaine is offered in the anhydrous, monohydrate and liquid form.

. . . market

The price level of betaine has decreased constantly throughout the past 10 years (see Table 2.48). In Europe, the monohydrate form was sold in 1999 at DM 3.45–DM 4.50 per kg. The anhydrous betaine is approximately 20% more expensive.

Table 2.48: Price development of betaine, 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
$/kg	2.40	2.55	2.75	3.25	4.30	4.35	5.40

*Note: * First quarter*

The global sales of betaine to the feed market are estimated at $27 million for the year 1999. It is predicted that the market for betaine will grow at 3% per annum. Prices may further weaken over the next few years due to increasing competitive pressure from Asia.

. . . companies

Major suppliers for the feed sector are the companies Danisco (ex Cultor-Finnfeeds) from Denmark and Ducoa from the US. Betaine from China is also available. The former Goldschmidt group has been taken over by SKW-Trostberg, which merged with Degussa-Huels in October 2000.

Table 2.49: Market share of betaine manufacturers, 1999

Global market	10.5 tonnes
Manufacturer	**% market share**
Danisco	65
DuCoa	26
SKW-Trostberg	<1
Other	8

2.2 Auxiliary substances

Auxiliary substances are constituents or preparations that have beneficial effects on the quality of the feed, the excreta or the animal's end product. Feed quality improvement may cover freshness, technological properties and organoleptic characteristics. Conditioning of feed with the help of auxiliary substances aims in all cases at non-nutritional effects.

2.2.1 Carotenoid pigments

Carotenoids are pigments of yellow, orange or reddish colour.

They are ubiquitous in nature but are synthesised only by plants and microorganisms. Chemically, carotenoids are a class of hydrocarbons (carotenes) and their derivatives (xanthophylls). They are derived from the acyclic $C_{40}H_{56}$ structure, having a long central chain of conjugated double bonds. More than 600 carotenoids have been isolated from nature.

In the feed industry xanthophylls are used as pigmenters in animal production. The only exception to this is betacarotene which can be used in shrimp to achieve the desired pinkish colour. This use application, however, is not promoted by the major carotenoid producing companies. Animal species of higher order are dependent on the external supply to cover their needs for pigmenting and biological functions.

Depending on the desired pigmentation colour, the industry offers pigmenting agents of yellow and red colour.

2.2.1.1 Yellow pigments

Provide a yellow-pigmenting effect in egg yolk and broiler skin.

. . source

There are two types of yellow carotenoids available on the market; pigments from chemical synthesis and natural products. The synthetic yellow carotenoid apo-ester (chemical name: β-apo-8'-carotenoic acid ethyl ester) is manufactured from a base molecule. The natural pigment is extracted from xanthophyll-rich plants, the main source being the tagetes flower. The flower is grown for the yield of the two xanthophylls; lutein and zeaxanthin.

. . forms and formulations

Most commercial products are offered within a range of 1%–3% activity. Products are formulated in powder, oil and water-miscible forms.

. . . market

The major countries which grow tagetes for pigmentation products are Mexico, Columbia, China and India.

Prices for yellow xanthophylls have dramatically decreased over the past 10 years (see table 2.50). In early 2000 the average cost per 1g of tagetes xanthophylls was $0.23 compared with $0.90 in 1990.

Table 2.50: Price development of yellow xanthophylls from tagetes flower, 1992–2000

Year	2000	1999	1998	1997	1996	1995	1992
$/g	0.25	0.23	0.25	0.28	0.30	0.24	0.90

The global sales volume of natural yellow xanthophylls in 1999 was approximately 270 tonnes. Future annual growth is estimated at 2.5%.

In recent years, apo-ester prices had to be reduced due to growing price competition from natural products (see Table 2.51). The global market share also deteriorated from above 50% before 1990 to about 12% in 1999.

Table 2.51: Price development of apo-ester, 1990–1999

Year	1999	1998	1997	1996	1995	1990
DM/kg apo-ester	1350	1500	1950	1830	1850	1600

The global sales of apo-ester in 1999 were approximately 19 tonnes. Future annual growth until 2004 is estimated at 2%.

. . . companies

Apo-ester is produced and sold by the two multi-national companies Roche and BASF. Both companies sell their products in a protected granular form with 10% concentration in activity.

Table 2.52: Sales of apo-ester by manufacturer, 1999

Manufacturer	kg
Roche	13,500
BASF	5,500

2.2.1.2 Red pigments

All products have their advantages and disadvantages in terms of use application. They differ regarding pigmenting efficacy, colour hue, product stability in feed processing and absorption in the digestive tract. Like other carotenoids, they have a variety of biological functions including provitamin A.

Other biological functions suggested for astaxanin are:

- Essential nutrient in salmon fry
- Antioxidative action
- Function in reproduction process
- Involved in cell communication

. . . source

Canthaxanthin is mainly found in the orange-coloured mushroom *Cantarellus cinnebarinnus* and capsanthinis is derived from red capsicum. Competing against these in the market for poultry feed additives are a synthetic form of canthaxanthin and another synthetic product, citranaxanthin.

Natural astaxanthin is derived from the micro-algae *Haematococcus pluvialis* and the yeast *Phaffia rhodozyma*; it is used in aquaculture feed and is also available in synthetic form.

. . . application

Almost all red pigments are used in poultry feeding to provide a orange colouration of egg yolk, but approximately 15% of all canthaxanthin produced is added to salmon and trout feed.

The primary reddish pigment in salmon, trout and crustaceans is astaxanthin, the carotenoid found in tissue and skin of wild fish and shrimp. The pinkish colour is linked to quality and is a major criteria in the buying decisions of consumers.

. . . forms and formulations

The synthetic carotenoids are sold in a stabilised form of 10% concentration. Capsanthin is marketed in concentrations of 0.5%–3%. Like yellow tagetes xanthophylls, capsanthin products are formulated in powder, oil and water-miscible forms.

2.2.1.3 Poultry industry

. . . market

The actual global market for the three main red pigmenting products is estimated at around 110 tonnes of pure carotenoids. A breakdown by different product groups is given in Table 2.53.

Table 2.53: Global market for red pigments

Pigment	kg
Capsanthin	20,000
Canthaxanthin**	81,000
Citranaxanthin	9,500

*Note: * aproximately 15% of all cathaxanthin produced is added to salmon and trout feed*

The price level for canthaxanthin, has been relatively stable throughout the past 10 years (see Table 2.54). This is explained by the dominant role of Roche as the main supplier for red pigments. In the Americas and in the Far East canthaxanthin was priced in the range of $1,600 per kg in 1999.

Table 2.54: Price development of canthaxanthin, 1990–1999

Year	1999	1998	1997	1996	1995	1990
DM/kg	2220	2260	2320	2440	2420	2200

The natural pigment capsanthin is sold at around $1900 per kg ai. Altogether the global sales value of all red pigmenting additives for poultry is close to DM 250 million.

. . . companies

Major producers of red carotenoids are given in Table 2.55.

Table 2.55: Major manufacturers of red pigments

Manufacturer	Pigment	Sales (kg)
Roche	Canthaxanthin	67,000
nature*	Capsanthin	21,000
BASF	Canthaxanthin	14,000
BASF	Citranaxanthin	9,500

*Note: * Major companies, which extract capsanthin from capsicum are: Pigev/Mexico, Bioquimex Reka/Mexico, Industrial Organica/Mexico*

2.2.1.4 Fish and shrimp industry

. . . market

More than 80% of all red pigments used in aquaculture are in the form of synthetically manufactured astaxanthin. Canthaxanthin has a share of approximately 15%.

The price level of astaxanthin is traditionally dominated by Roche. After pioneering the development and introduction of the product in the mid 1980s, they enjoyed an uncontested leading position until 1999. The pricing strategy for the recently introduced microbially derived astaxanthin follows that of Roche. Sales price of astaxanthin was kept at DM 4,000 per kg throughout the past 10 years (see Table 2.56). During the same period, dollar prices fluctuated around $2,600.

Table 2.56: Price development of astaxanthin, 1990–1999

Year	1999	1998	1997	1996	1995	1990
DM/g	3,900	3,920	3,940	3,940	4,060	3,900

The global sales of astaxanthin developed in line with the worldwide growth success of the salmonid industry. From the date of introduction in 1985 to date, astaxanthin demand grew at annual double-digit percentage rates. The global sales volume was above DM 500 million in 1999.

Astaxanthin demand is forecast to grow at a 10–20% rate per annum throughout the coming five years.

. . . companies

To date Roche and BASF are the only suppliers of synthetic astaxanthin (see Table 2.57). BASF entered the market when the astaxanthin patent expired in 1999. Roche supplied the ai to BASF until the end of 1999. Since then BASF has started its own production.

Natural ataxanthin is produced in North America by Cyanotech, Igene Biotechnology Incorporated and Aquasearch Incorporated and in Sweden by AstaCarotene AB. Ventures in Japan, Spain and Australia have announced the introduction of new commercial products. The Dutch company DSM and the US-based company Universal Food sold their technology – including their product inventories, to Roche, which soon afterwards withdrew both products from the market.

Table 2.57: Main manufacturers and sales of astaxanthin, 1999

Manufacturer	Sales (kg)
Roche	120,000
BASF	8,000
Natural astaxanthin*	5,000

*Note: * Various companies in North America and Sweden*

2.2.2 Antioxidants

Antioxidants inhibit oxidation processes in fats and oils. Free radicals are formed in the early stages of fat oxidation which can initiate chain reactions, ultimately resulting in a rancid smell and taste of fats. The antioxidants can block the oxidation process by scavenging the free radicals.

Fatty acids and other fat-soluble nutrients are prone to oxidation. This process can be effectively retarded by the addition of antioxidants. Required dosage levels are directly related to a number of factors including duration of feed storage, degree of storage temperature, presence of oxygen, light exposure and presence of metal ions. The higher the oxidative reactivity, the more antioxidants must be added to protect the fat from deterioration. Antioxidants are used up over time and are not recycled.

. . . source

Antioxidants can be subdivided into two groups. The commonly used class of products is synthetic such as ethoxyquin, butylated hydroxylanisole (BHA) and butylated hydroxytoluene (BHT). Natural antioxidants derived from vitamin E and C are expensive and rarely used in feed applications.

. . . application

Rendering fats and oils are generally supplemented with antioxidants at the time of production. Other feeding stuffs with substantial fat content are also blended with the radical scavenger. Depending on the composition of premixes and compound feeds some addition of antioxidants is required. In summer time the chemical reactivity is increased, which requires generally higher levels of antioxidant addition. Fat-soluble vitamins contain some antioxidants in their formulation.

Another antioxidative strategy that is applied is to extend the shelf life of meat products. This can be achieved by using α-tocopherol (vitamin E) as an internal antioxidant. Scientific data on broiler, cattle, pigs and salmonids reveal that addition of vitamin E to the feed of fattening animals delays the initiation of rancidity processes in meat. The idea is strongly promoted by some of the major manufacturers of vitamin E. Despite a large number of positive scientific results and many years of marketing campaigns, few feed producers have adopted this strategy. Consumers and supermarkets prefer fresh meat, short storage time on shelf and a fast turnover of goods. Additionally, nobody in the production chain is willing to bear the extra cost for the feed additive.

. . . forms and formulations

All products are generally approved for use in farm animals.

. . . market

Synthetic antioxidants are fairly inexpensive products. They are sold at $1.00–$3.00 per kg. Blends of various antioxidants are usually sold at premium prices. As only around 50g–200g of antioxidants are added per tonne of feed, application costs are in the range of $0.05 to $0.60 per tonne of feed. Prices for standard products such as ethoxyquin, BHA and BHT have not changed much in the past years. Branded products are frequently offered on the market

but as they hardly provide superior results over generic goods, their market share is modest. The market share for natural antioxidants is negligible.

The antioxidant market comprises of about 35,000 tonnes of ethoxyquin, BHA and BHT. Natural antioxidants account for around 1% of the total volume. The market is anticipated to grow at an annual rate of 2–3% till 2004. In value, the global market was worth approximately DM 131 million in 1999. Sales turnover will not grow till 2004, as the volume increase is expected to be offset by decreasing prices.

Table 2.58: Global sales of antioxidants by region, 1994–2004

Year	1994	1999	2004
% sales by region			
Europe	47	44	41
Americas	33	37	37
Asia	14	13	16
RoW	6	6	6

. . . companies

The antioxidant market has a multitude of manufacturers. Most of them have only local or regional sales representations. None of the global players has yet achieved a dominant market share in the feed sector. Prominent manufacturers and marketers of antioxidants acids are listed in Table 2.59. The atomised market structure means that no market share figures can be given.

Table 2.59: Major manufacturers and marketers of antioxidants

Manufacturers/marketers
Aventis – France
Bayer – Germany
Helm – Russia
IPSA – Spain
Kemin* – US
Lohmann – Germany
Lucta – Spain
Marshall Thomas Company – US
Monsanto-Novus – US
Philipp Brothers Chemicals – US
Raschig, Germany
Selco, Sweden

*Note: *Purchase straight antioxidants and sell blended products*

2.2.3 Taste and flavour substances

Taste and flavour substances are organic and have characteristic smell and taste properties. They have no nutritional value but may improve organoleptic appeal. They can add taste or cover the smell of feeds.

Compound feeds can be standardised and improved in taste by supplementing with highly palatable substances. Flavour can also be added to mask unfavourable smell of feeds. Sales companies claim that the application of flavours makes the feed more palatable and subsequently, animals consume more feed and grow faster. Critics claim that flavours are added to psychologically influence the purchasing decision of farmers. Branded feeds have a distinctive smell that farmers associate with freshness and quality and which makes each brand recognisable

. . . source

Taste and flavour substances are classified in two groups:

Substances occurring in nature. The main products are fruit esters, glutamates and vanillin. The number of authorised products is vast. More than 200 individual products are known on the market. Together with all combined and blended products the number becomes immense. There are no restrictions on application as yet, regarding animal species, dosage or age of animals. The substances can be of natural or synthetic (so-called natural identical) origin.

Synthetic products include saccharin, its salts and neohesperidine dihydrochalcone.The use of these products is regulated by the EU feed legislation, by animal species, concentration in feed and age of animals. Saccharin in piglet feed, for example, is approved only up to the age of four months. Maximum content in complete feed is limited to 150mg/kg. For other substances different levels apply.

. . . application

Taste and flavour substances if used at all, are mostly applied in young animal feeds . The benefit claimed by the manufacturers is earlier weaning of piglets and calves. Feed intake is also said to be improved.

. . . market

The large number of products and suppliers is reflected in a wide price variation. In addition, many taste and flavour substances are sold in blends. This makes them more unique and less price sensitive. Prices of pure substances have not changed much over the past 10 years. Prices vary between \$2.00–\$6.00 per kg depending on the type and concentration of single ingredients and mixture. Dosages for concentrated products range from 30g–200g per tonne of feed.

Market penetration with taste and flavour substances varies a lot between countries (see Table 2.60). The major use applications are in piglet and calf feeds. It is common practice to add taste and flavour substances to companion animal feeds. Europe is the main market for non-nutritive additives. Germany and the UK are the leading markets within Europe.

Table 2.60: Percentage market penetration for taste and flavour substances, by country

Animal category	Dairy cows (%)	Calves (%)	Beef cattle (%)	Sows (%)	Piglets (%)	Fattening pigs (%)	Poultry (%)
Germany	75	65	55	35	90	10	0
UK	55	85	0	0	100	0	0
Nordic Countries.	80	90	65	45	90	25	0
France	10	75	15	25	90	10	0
US	<10	60	0	20	80	<10	0
Taiwan	60	90	40	55	90	25	0
Brazil	<10	25	<10	<10	60	<10	0

The global market for taste and flavour substances is estimated at 20,000 tonnes, of which 50% is consumed in Europe. The market is worth approximately $70 million. The global consumption and sales prices are generally stable and the market value is expected to persist over the next five years.

. . . companies

The market has numerous suppliers of taste and flavour substances. None of the basic manufacturers or marketers has yet achieved a prominent market position in the feed sector. On a global basis, market shares of the listed companies are between 2 and 7%. Major companies are listed in alphabetical order in Table 2.61.

Table 2.61: Major manufacturers and marketers of taste and flavour substances

Manufacturers/marketers
Agil
David Moore
Dragoco/Micro Plus
Haarmann & Reimer/Gefachem
International Additives
Kemin
Lohmann
Lucta
Pancosma

2.2.4 Emulsifiers

Emulsifiers are substances which enable the formation of stable mixtures of different liquids, such as blends of water and oil. On a micro scale the emulsifier prevents the merging of dispersed droplets of one of the liquid. The smaller the dispersed droplets are, the better the stability of the emulsion.

Emulsifiers can be salts of higher fatty acids, lecithin, saponins, polysaccharides or other suitable substances.

. . . application

The use of emulsifiers is widespread in food production, but not in feed applications. Milk is probably the best-known emulsion in nature. The normally immiscible fat is distributed in fine droplets in the aqueous milk liquid. This type of fat in water emulsion is also used in the production of milk replacers. The emulsifier enables a stable miscible liquid to form.

Unlike milk, other types of complete feed do not require any emulsifiers. Some feed additives, like fat-soluble vitamins, require some emulsifier in the formulation process of feed grade material. Most emulsifiers are used in milk replacer feeds for calves and to a lesser extent for piglets, kids and other species. Lecithin is also used in shrimp formulations in large amounts, exceeding the quantities used for emulsions, but the application in shrimp diets is for nutritional purposes and is therefore is not included when considering emulsifiers.

. . . market

The global market for emulsifiers in 1999 was about 185,000 tonnes, of which less than 20,000 tonnes were consumed by the milk replacer industry. The global market for milk replacers equals about 2–3 million tonnes dry powder. The proportional cost of emulsifiers in overall feed cost is low. Prices for emulsifiers range from \$0.50–\$1.00 per kg. Inclusion levels can vary from product to product between 100g up to 6kg per tonne of feed. Overall, the global market is estimated to be below \$10 million. 40% of the turnover is generated in Europe, 30% in the US and the rest is spread over the rest of the world. More than 90% of that turnover is generated with emulsifiers for calf milk replacers.

With the occurrence of several calf meat scandals in the past 15 years, the industry in Europe has been constantly shrinking. The small recovery in calf meat production in recent years resulted in some sizeable growth in the industry. It is anticipated that the competitive price pressure will compensate for the growth in emulsifier use. Thus, the sales turnover of emulsifiers will remain stable until 2004.

2.2.5 Organic acids

All acids with a carbon framework are referred to as organic acids. They include propionic acid, fumaric acid, formic acid, citric acid and acetic acid. Most acids occur in the metabolism and they can be used by the animal as a source of energy.

Organic acids are used in the feed industry for two purposes. One is for preservation of feeding stuffs and compound feed. Feeding stuffs include ensiled plant material and, in limited cases, raw fish mash. The second main application is a nutritional one, as the acids act directly on the digestive system and microbial population in the gastrointestinal tract of the animal.

The nutritional effects of organic acid use are explained as assisting the animal in maintaining a low pH in the stomach. It is scientifically accepted that organic acids lower the buffering capability of the feed in the stomach. Other more controversial marketing claims are:

- They have a selectively antimicrobial action
- They help amino acid digestibility

- They reduce formation of polyamins and ammonia in the large intestine.

. . . application

The preservation of feeding stuffs and compound feed can extend the storage time by reducing the microbial activity. All feeding stuffs are infested with moulds and bacterial organisms. They live on the energy and nutrients of the feed and produce toxins, which accumulate over time. Several factors, such as time of storage and moisture content, determine the development of microbes, which ultimately results in spoilage of feed. The process can be delayed by the addition of organic acids but acidification cannot reverse the deterioration process. The aim is to maintain the feed in a sufficiently good quality over a limited time period until feeding occurs. It is important to note that different microbial species react with different sensitivities to particular acids.

Mycotoxin accumulation resulting from mould growth in silage, feeding stuffs or compound feeds impairs animal performance. Microorganisms consume nutrients and energy and, at the same time, release mycotoxins, which decrease energy and nutrient availability and cause damage to the liver and kidneys. Insufficient feed conversion, weakening of the immune system and reduced viability are common signs of intoxication.

. . . forms and formulations

Practical dosage of organic acids to feed is in the range of 1–2 kg per tonne of feed. In most cases this amount is sufficient. Unfavourable storage conditions and high moisture content may demand higher acid levels for preservation.

For nutritional purposes higher addition levels are required. Addition of 2–20kg acid per tonne of starter pig feeds gives improved feed conversion ratios. The range of addition level is related to the type of organic acid used and the commercial viability.

Organic acid products are sold in liquid and crystalline forms. Products are offered in straight form or in mixtures of various acids and their salts. Special precautions are required when handling the products and corrosive-resistant materials are compulsory in the storage and transportation systems. Organic acids, both in straight and mixed form, are widely approved around the world by the regulatory authorities.

. . . market

Prices for organic acids have been less volatile than many other feed additives. The acids are marketed as commodity products and are sold in bulk to a variety of industry segments including human food and the cement industry. Margins, therefore, are relatively small. To date, prices range from \$0.45 to \$1,00 per kg or litre of product. Specific acid mixtures may be priced up to \$5.00 per kg. In Europe, prices for formic acid were at a low of DM 0.75 per kg in 1999. By mid 2000, the price recovered to DM 0.95 and a further upward trend is expected.

The cost of preservation of feeding stuffs or compound feed is relatively inexpensive. In contrast, the cost of addition for nutritional purposes can become prohibitive. The supplementation of piglet feed is widely accepted. Application provides best zootechnical results and only a little feed is required. Beneficial effects in grower pigs are considered to be less commercially viable.

Animal numbers determine the global market growth for organic acid in the nutritional sector. With the recession in Asia and a relatively stable market in the rest of the world, the total market for organic acids has stagnated over the past few years. The recovery of the global pig industry will boost acid use. Further dynamic development is seen as a result of the ban on most feed antibiotics in the European Union.

The worldwide use of organic acids in feed was estimated at 330,000 tonnes for 1999. Future dynamic growth is limited by restricted production capacity. Although animal numbers in many parts of the world are not greatly increasing, an annual growth rate in the use volume of organic acid is estimated at 5% till 2004 (see Table 2.62). The major reason for the steady growth is seen as the safe and consumer friendly character of organic acids.

Table 2.62: Global sales of organic acids by geographical region, 1994–2000

Year	1994	1999	2004
Global sales turnover DM million	429	440	486
% market share by region			
Europe	36	37	38
Americas	30	29	28
Asia	26	27	27
RoW	8	7	7

The price level is anticipated to decrease at a moderate rate of 1% per annum till 2004. It is worth noting that prices for various organic acids differ. Liquid acids are cheaper than the dry products.

. . . companies

Market shares of producers in the feed market are difficult to estimate because organic acids have a widespread use application in basic chemistry and in other industries. An example is the cement industry which is a major user of formate. Depending on the different price levels prevailing in the various industries, products are generally sold to those markets where highest profit margins can be achieved. This can result in a temporary shortage of organic acids in a particular market segment. The major suppliers of organic acids to the feed industry are listed in Table 2.63.

Table 2.63: Major manufacturers and marketers of organic acids

Manufacturer/marketer*
BASF
Bayer
Verdugt (British Petroleum)
Degussa
Norsk Hydro

*Note: * Most of the organic acids are sold by local companies under their own brandname as straight products or in blends*

2.2.6 Anticaking agents

Anticaking agents are non-nutritional auxiliary substances, which improve the flow characteristics of other feed additives and mash feed material. The addition of flow aids improves the characteristics of fine powders and hygroscopic materials making them easier to pour.

. . . source

Two groups of products are mostly used as flow aids. These are silica and its various salts and the long chain fatty acid stearate. Silica may be of natural and synthetic origin. Natural silicate clay minerals are relatively simple to produce.

. . . application

The use of flow aids is commonly applied in the formulation of straight feed additives. The adsorbate form of vitamin E is a good example. Here, the flow aids fulfil two distinct functions. First, they act as a carrier in holding the vitamin E oil and, secondly, they maintain a free flow of the additive. The latter function is achieved by reducing the binding forces of the particles.

Excessive moisture can result in sticky and lumpy product characteristics. Silica is capable of absorbing large amounts of moisture and it therefore often used in hygroscopic materials, found in spray-dried feed additives. By absorbing moisture the flow aid helps to separate the solid particles and prevent lumping of the powder product.

Another major application of anticaking agents is in the production of premixes. Premixes are blends of one or more micro-ingredients with a diluent and/or a carrier. They are prepared prior to final mixing with feeding stuffs. Premixes must flow easily and facilitate a rapid and uniform distribution in feed. Flow aids help to overcome undesirable effects such as homogenous instability of the premix, formation of lumps and build-up of electrostatic charges. In some circumstances mash feed may also require the addition of anticaking agents.

. . . forms and formulations

Flow aids are normally added in a range of 0.5%–3%. In specific cases the additive can function as flow aid and as a carrier. In such cases the concentration can go up to 50%. The global market for the use of silica and stearates in the feed sector is estimated at 60,000 tonnes per annum.

. . . market

Table 2.64 shows global sales of anticaking agents.

Table 2.64: Global sales of anticaking agents by geographical regions, 1999

Global sales	60,000 tonnes
Sales by region	%
Europe	50
Americas	30
Asia	13
RoW	3

Prices for silica products vary according to quality and technical properties. Based on an average price of DM 0.50 per kg of flow aid material, the global turnover was estimated at DM 30 million for 1999.

2.2.7 Ammonia binder

Ammonia binders are added to compound feed to reduce the emission of ammonia from excreta.

. . . source

One nutritional approach to reduce the level of ammonia in animal buildings is by addition of ammonia binders to feed. The extract of the Central American cactus *Yucca schidigera* is used for this purpose. Scientific studies show that the water-soluble fraction of the *Yucca* extract can effectively bind ammonia. The binding effect peaks a few days after a single application and decays thereafter. Under practical conditions it is applied continuously in feed. Buffering of ammonia in the digestive tract by *Yucca schidigera* is claimed also to improve protein utilisation, to increase feed conversion and, as a consequence, to result in a better daily weight gain.

Another method of absorbing ammonia is by the addition of clay minerals to the feed, this has not been discussed as the technology involved is relatively simple.

. . . application

In intensive animal production more than 50% of all consumed protein-nitrogen is excreted in faeces and urine. The control of litter and dung quality is important for effective management of animal production. Ammonia is produced by microorganisms from metabolism of undigested proteins in excreta or urine. Ammonia evaporates, accumulates in the surrounding air and, if it is not properly removed, ultimately results in health problems and depression of farmed animal productivity. Concentrations above 25ppm ammonia in the air are known to cause growth depression. Higher concentrations of above 50ppm may facilitate infection with disease causing microorganisms and impair general immune response.

Diets high in protein content generally create more atmospheric pollution problems. This is particularly the case with pigs and poultry. Higher temperatures support microbial activity in the excreta and, hence, formation of ammonia. Moisture content is also positively correlated with microbial activity. In wintertime poor ventilation is often practised for cost-saving reasons. This leads to additional accumulation of ammonia.

. . . market

Ammonia binders first became popular on the US market and in the UK (see Table 2.65). Legal restrictions in the EU hampered a fast penetration of further European markets. Ammonia binders are still sold at a premium price level. With the entrance of several other natural ammonia binding products a downward price trend is anticipated.

Table 2.65: Development and consumption of ammonia binders by region, 1996–2004*

Year	1996	1999	2004
Total market (tonnes)	240	245	250
% market share by region			
US	33	37	36
UK	19	16	16
Denmark	15	13	10
Rest of EU countries	19	16	16
Asia	8	14	18
RoW	6	4	4

*Note: * Based on Yucca schidigera*

The global demand for ammonia binders is growing slowly. The production crisis of the pig industry in the past years has hampered further volume growth. Low pig prices forced farmers to purchase low-cost feed. Subsequently, several feed suppliers withdrew non-essential additives from their feed.

The volume of ammonia binders will grow at an annual rate of 1% till 2004. Prices are anticipated to decrease by 20% during the same period. This will reduce the value of the global market from $2.5 million in 1999 to $2.0 million in 2004 (see Table 2.66).

Table 2.66: Price development and global market value of ammonia binders, 1996–2004*

Year	1996	1999	2004
Price per kg, $	15.00	10.00	8.00
Sales value, $million	3.6	2.5	2.0

** based on Yucca schidigera*

. . . companies

The relatively small sales turnover is shared by a number of companies, which are given with their estimated market shares in Table 2.67.

Table 2.67: Market share of ammonia binder producing companies, 1999*

Manufacturer	% market share
Desert King	25
MicroAid	20
Alltech	15
NorFeed	10
Kemin	7
Ducoa	5
Others	18

*Note: * on the basis of* Yucca schidigera

2.2.8 Mycotoxin binders

Mycotoxin binders are feed additives with a high affinity to absorb toxins previously released from microorganisms. Binder substances are of a porous structure. Mycotoxins are caught in the pores and subsequently excreted together with the binder material before they can cause intoxications in the animal.

Mycotoxins are a global problem with regard to animal productivity. Mould growth in feeding stuffs and feeds cause serious adverse effects on:

- Growth rate
- Feed conversion
- Function of liver and kidneys
- Bone formation and
- Disease resistance

. . . application

The addition of sorbent materials is widely practised in the feed industry around the world.

. . . forms and formulations

Most of the antitoxic binders can be classified as aluminium silicates. This generic term refers to:

- Layered silica minerals or clays
- Highly porous zeolites

Both types of minerals contain aluminium (Al_2O_3) and silica (SiO_2). Another binder, which does not fall in this class of products, is activated charcoal.

Mycotoxin binders vary widely in their composition. Depending on their origin, the natural silicates differ markedly in their mineral content, their porous diameter and in their binding capacity. The latter being the important factor that provides protection against mycotoxin intoxications.

There is well-documented literature on the subject of binding capacity of various aluminium silicates to mycotoxins. The scientific results refer to *in-vivo* and *in-vitro* studies. Most

studies have attempted to test the binding capacity for a particular mycotoxin. Results from any study conducted with a particular mycotoxin cannot be extended to another toxin. This is because of the characteristic molecular structure of toxins which have distinct binding affinities. Specific aluminium silicates, on the other hand, have particular binding affinities to different mycotoxins. Therefore, extension of defined *in-vitro* and *in-vivo* studies to practical feeding is limited.

Another strategy to de-activate mycotoxins in the digestive tract is the use of enzymes and yeast cell wall products. Neither strategy has been widely accepted in the industry.

The low cost of production of clays and zeolites has motivated many companies to offer branded materials as a preventive to mycotoxicosis. There is a large number of commercial products and no company has achieved any substantial global market share for this type of feed additives.

. . . market

Mycotoxin binders are sold both at extremely low and at premium price levels. In the latter case, silicates are combined with other additives to distinguish them from common clay products. The price of these combination products fluctuates less, but comparing costs of the different products available is more difficult.

The global market for mycotoxin binders is estimated at around DM 34 million. The volume growth is forecaste at a rate of 5–10% per annum. The increasing demand is a result of increasing awareness of mycotoxin contaminations in feeds. This has been triggered by better analytical procedures and more sophisticated technologies leading to decreasing analytical costs and faster analysis. The market itself will continue to develop in two separate segments, the high-priced value added products and the cheap commodity clay products.

2.2.9 Pellet Binders

Pellet binders are auxiliary substances that are used in feed compacting. Typical compacting processes are pelleting and extrusion. The use of pelleting binders is necessary to facilitate durability of feed, to overcome the poor compacting characteristics of some of the cheaper raw materials and to increase the throughput of feed in the mill. In addition, feed compositions are constantly changing due the to price fluctuations of feeding stuffs.

Feed dust is formed by mechanical stress and abrasion of pellets. Dust is wasted feed for the farmer and represents a health risk to animals. Adverse effects apply both for land-based animals and to aquaculture species. In the latter case, feed dust will result in eutrophication and pollution of the surrounding water, leading to oxygen deficit and mortality of cultured fish and shrimp.

As well as the binding effect, pelleting additives can also lubricate the feed ingredients while passing through the compaction die. The reduction in energy required to compact the feed and improve production rate can recoup the cost of the binder.

. . . application

Pellet binders are generally applied in aquaculture feeds for slow eating species. Diets with high crude fat levels also require the addition of pelleting aids. Finally, feed blocks and pellets of larger size require the auxiliary substance to form a durable product.

. . . forms and formulations

Several feeding stuffs, including wheat gluten, molasses, alginates and plasma proteins are known to improve the durability of pellets.

There are many pellet binders on the market. Products can be grouped into

- Lignosulphonates
- Carboxymethylcellulose
- Aluminates
- Chemical polymers
- Urea formaldehyde resin

Levels of addition for non-nutritional binders are mostly in the range of 2.5–50 kg per tonne of feed. Products with lower inclusion levels have an advantage insofar as they allow more room for nutritional ingredients. Not all binders are compatible with all feed compositions.

. . . market

Inclusion costs of non-nutritional binders are in the range of $0.20–$3.0 per tonne of feed. The global turnover for pellet binders is estimated at $33 million. The volume growth throughout the next five years is forecasted at 5% per annum.

. . . companies

Major suppliers of

Table 2.68: Major manufacturers/marketers of pellet binders

Manufacturers/marketers
BASF – Germany
Georgia Pacific Chemical Products – US
Industrial Grain Products – US
ISP – Europe
Lafarge – France
La-Roquette – France
Lignotech – US
Uniscope Incorporated – US

2.3 Digestive enhancers

This chapter deals with a variety of feed additives, which all act on the digestive capability of the gastrointestinal tract system. All these feed additives claim to benefit feed utilisation and to enhance the animal's performance. Although some use applications of organic acid would also fall into this category, this product type is dealt with under auxiliary substances. This is because the majority of organic acids are applied for feed preservation rather than performance enhancement.

2.3.1 Antibiotic performance enhancers

Antibiotic performance enhancers are antimicrobial agents produced by fermentation or through chemical synthesis. They are added to compound feed to improve the animal's feed utilisation during growth phase. Antibiotic performance enhancers are also referred to as growth enhancers, growth promoters and growth permitters. Although the general growth effects are not much disputed, they are neither constant nor predictable. In fact, repeated studies seldom show comparable results. The growth enhancement is generally more pronounced in young animals than in older animals. Their beneficial effects are observed in cattle, poultry, pigs, fish and other animals.

Antimicrobioal drugs and performance enhancers are of the same class of substances which can cause confusion. The distinction is that antibiotic performance enhancers are governed by feeding stuff regulations and are used to improve the animal's performance whereas antimicrobial drugs:

- Are applied to cure/prevent acute diseases
- Are used in higher daily amounts
- Are regulated by medicinal laws

In the EU, antimicrobial substances used for therapy in feed fall under medicated feed law, which is part of the law on veterinary therapeutics. This is not the case in the US.

2.3.1.1 Cattle

In fattening cattle with a functional rumen antibiotic ionophores are generally approved for feeding. Monensin obtained clearance approximately 25 years ago. Lasalocid under its brand name bovatec appeared just seven years later, but it never obtained approval in the EU. Both ionophores were originally marketed to enhance growth by changing the volatile fatty acid pattern in the rumen in favour of propionic acid. Later it was shown that they also inhibit lactate and ammonia-producing ruminal bacteria. In 1994 another ionophore, laidlomycin, was approved in the US. It is claimed that this ionophore also controls bloat problems. All products are also active in controlling acidosis and coccidiosis problems. Other products,which are frequently used in the US, include flavomycin, avoparcin, virginiamycin and bacitracin.

Antibiotic growth enhancers for fattening cattle are listed in Table 2.69.

Table 2.69: Antibiotic performance enhancers used in fattening cattle

Manufacturer	Generic name	Trademark
Alpharma/Roche	Avoparcin *	Avotan
Alpharma/Roche	Lasalocid	Bovatec
Alpharma	Bacitracins	Albac/BMD
Alpharma/Roche°	Chlortetracycline	Aurofac°
Intervet/ Höchst	Flavophospholipol	Flavomycin
Alpharma/Roche	Laidlomycin	Cattlyst
Elanco	Monensin	Rumensin/Romensin
Koffolk/Pfizer	Virginiamycin	Stafac

*Note: * Discontinued production end of 1997; °Branded products from several other manufacturers available*

2.3.1.2 Pigs

The production of pig feed has declined in the past few years due to the swine crisis in Europe and elsewhere. Since the EU ban of avoparcinin in 1996 and of six performance enhancing substances out of nine in 1999, many farm operations in Europe now grow their pigs successfully without use of antibiotics.

A list of the most frequently used antibiotic performance enhancers in pigs is given in Table 2.70.

Table 2.70: Antibiotic performance enhancers used in pig feed

Manufacturer	Generic name	Trademark
Elanco	Avilamycin	Maxus
Alpharma/Roche	Avoparcin *	Avotan
Alpharma	Bacitracins	Albac/BMD
Alpharma/Roche °	Chlortetracycline	Aurofac°
Intervet/Höechst	Flavophospholipol/bamberycin (US)	Flavomycin
Pharmacia & Upjohn	Lincomycin	Lincomix
Several	Oxytetracycline	Several
Several	Penicillin	Several
Intervet/Höchst°	Salinomycin	Sacox°
Aventis	Spiramycin	Spiramix
Novartis	Tiamulin	Tiamutin
Elanco	Tylosin	Tylan
Koffolk/Pfizer	Virginiamycin	Stafac

*Note: * Discontinued production end of 1997; ° Branded products from several other manufacturers available*

2.3.1.3 Poultry

In poultry, great advances were achieved in improving feed conversion and in reducing grow-out period for broilers. This development was supported by the wide use of antibiotic performance enhancers. In adult poultry they improve egg production and hatch rate.

The main products are listed in alphabetical order by their generic name in Table 2.71.

Table 2.71: Main antibiotic performance enhancers used in broiler feed

Manufacturer	Generic name	Trademark
Koffolk/Pfizer	Ardacin	
Elanco	Avilamycin	Maxus
Alpharma/Roche	Avoparcin *	Avotan
Alpharma	Bacitracins	Albac/BMD
Alpharma/Roche °	Chlortetracycline	Aurofac°
Intervet/Höchst	Flavophospholipol	Flavomycin
Pharmacia & Upjohn	Lincomycin	Lincomix
Several°	Oxytetracycline	Several
Several°	Penicillin	Several
Novartis	Tiamulin	Tiamutin
Koffolk/Pfizer	Virginiamycin	Stafac

*Note: * Discontinued production end of 1997; ° Branded products from numerous manufacturers available*

2.3.1.4 Other species

Antibiotic additives are listed as performance enhancers in may countries for a wide range of animal species. They include fish, shrimp, fur-bearing animals, waterfowl, rabbits and pigeons. In the EU, some performance enhancers are allowed for other poultry with the exception of duck, geese and pigeons.

... forms and formulations

Manufacturers of generic feed antibiotics have claimed a relevant share of the market to date. Several antibiotics are offered today by a multitude of companies. Therefore, trade names have been given only for those original antibiotics that still dominate the market. Trade names, claims and use of product combinations varies between countries and geographical regions. The listing of all this information alone would fill a market survey study.

Most of the branded products are sold in pre-blended formulation. The premixes generally contain 1%, 2%, 5% 10% or 15% of the ai, Tylan contains up to 25% ai and Stafac 50% ai. Some feed regulations demand sales of feed antibiotics in pre-mixed form only to avoid health hazards in the feed mill operation. Producers of generic products, mainly from China, also offer antibiotics in the pure form. Examples are salinomycin and tetracyclines.

... market

Several antibiotics, which are approved in pig and poultry feed, are also used in calf nutrition. Within the EU, the ban of antibiotic feed additives resulted in a withdrawal of virginiamycin, zinc bacitracin, spiramycin and avoparcin in milk replacers. All of them were frequently used until 1998/1999. The ban of these products has resulted in dramatic change of the feed antibiotic market in Europe.

A limited number of products dominate the global market for performance enhancers. Six feed antibiotics account for more than 50% of the global market. The market for antibiotic performance enhancers was rather static until 1998. With the recent ban of several antibiotics in the EU, the global market has declined. The European market has shrunk by 50% but in the rest of the world product sales are still growing. Altogether the global sales turnover has fallen by approximately 15% since the ban.

The most significant effect on the use of antibiotics in 1999 was caused by the ban of four growth promoters by the EU authorities. Tylosin, virginiamycin, spinamycin and bacitracin were all suspended due to concerns that use in animal production may impair the efficacy of some antibiotics used in human medicine. The ban came into effect from July 1999. This was preceded by the ban on avoparcin in December 1996. Antibiotics in use are reduced to flavomycin and avilamycin.

Another impact of the EU ban is the unwillingness of the industry to invest capital in the development of new products.

Prices for antibiotic performance enhancers has been decreasing over the past 10 years. In total, the market volume is difficult to estimate, since there is a grey market, particularly in the developing countries where product use is often unrestricted. See Tables 2.73 and 2.74 for an outline of the market in 1999.

Table 2.72: Price levels and inclusion cost of selected antibiotic performance enhancers, 1999

Generic name	Price ($/kg ai)	Inclusion level g/tonne	Cost ($/tonne feed)	Animal species*
Lasalocid	35.00	50	3.20	p, f
Bacitracins	22.00	50	2.40	p, c, f, s
Monensin	35.00	50	2.50	p, c, f, s
Avilamycin	128.00	40	5.10	p
Salinomycin	69.00	60	3.20	s
Tylosin	80.00	50	5.00	s
Virginiamycin	95.00	50	4.60	p, s
Chlortetracycline	20.00	50	1.90	p, c, f, s

** p=poultry, c= calves, f= fattening cattle, s=pigs*

Table 2.73: Global production, branded product concentrations and brand names for selected antibiotic performance enhancers, 1999

Generic name	Brand name	Global production (tonnes of a.i)	% concentration
Bacitracins	Baciferm, Albac, BMD	2,500	12
Chlortetracycline	Aureomycin°	4,500	10, several others
Lasalocid	Avatec, Bovatec	1,400	15, 20
Monensin	Coban°	1,300	8
Salinomycin	Bio-Cox°	1,400	6, 12
Tylosin	Tylan°	1,300	10, 25, 33
Virginiamycin	Stafac	550	5

Note: ° Other branded products are available on the market

Table 2.74: Global market for antibiotic performance enhancers ($ million)

Generic name	1994	1999	2004
Bacitracins	88	76	70
Chlortetracycline	150	80	75
Monensin	65	75	60
Oxytetracycline	130	66	60
Salinomycin	95	82	75
Tylosin	130	89	40
Others	392	451	410
Total	1,050	919	790

In Tables 2.75 and 2.76, an attempt is made to break down the sales turnover by major geographical region and by animal category. The first table provides figures for 1994 and the next one for 1999.

Table 2.75: Use of antibiotic performance enhancers by animal species and geographical region, 1994

Region	Poultry	Pigs	Calves	Cattle	Others	Total
European Union	135	190	7	8	25	365
North America	200	170	2	55	18	445
RoW	135	80	1	12	12	240
Total	470	440	10	75	55	1,050

Table 2.76: Use of antibiotic performance enhancers by animal species and geographical region, 1999

Region	Poultry	Pigs	Calves	Cattle	Others	Total
European Union	120	45	2	1	28	196
North America	210	160	3	50	20	443
RoW	158	91	1	15	15	280
Total	488	296	6	66	63	919

There has been a shift from red meat to poultry in most developed countries over the past 10 years. In emerging markets poultry production is also generally growing fast. This has resulted in a worldwide increase of broiler production.

The future development of antibiotic performance enhancers is quite unclear. There are already signs that other countries will follow the EU in banning several or all antibiotic performance enhancers. Countries with an export oriented broiler and pig industry have already selectively stopped using feed antibiotics in animals to be exported to Europe. Since the debate about the feed antibiotics causing the resistance build-up of bacteria in humans has begun in many other countries, it can be anticipated that the total market will further decrease. This may be driven by legislation or a voluntary decision by the meat industry.

The decision by the EU authorities has initiated a worldwide discussion. Although the World Health Organisation (WHO) together with other organisations, set up expert committees, it is still a matter of controversy as to whether feed antibiotics are responsible for the build-up of resistance to antimicrobials in humans. It appears that consumer opinion rather than proven scientific fact is influencing political decisions against the further use of feed antibiotics.

. . . companies

The industry for antibiotic performance enhancers has been shaken by dramatic change and is in the process of restructuring. Threatened by the EU decision, several companies have downsized or even terminated their R&D activities in the field of antibiotic performance enhancers. Roche has sold its medicinal feed additive business to Alpharma and Pfizer made a deal with Israel-based company Koffolk in early 2000, signalling a reassessment of product strategies and a consolidation of the whole industry. In the US Pfizer has sold its feed additive business to Phibro Animal Health, a division of Philipp Brothers Chemicals (Animal Pharm 454, 6 October 2000, p 17).

2.3.1.5 Non-antibiotic performance enhancers

Non-antibiotic performance enhancers are mostly marketed for use in pig and poultry feeds.

Technical-scientific promotion of product use cover arguments for growth enhancement and health claims such as:

- Protection against swine dysentery (roxarsone, arsenilic acid)
- Protection against salmonellosis in pigs (carbadox)
- Protection against enteric disease in pigs (olaquindox)
- Improved pigmentation in poultry (roxarsone).

. . . forms and formulations

A list of the most important products is given in Table 2.77.

Table 2.77: Non-antibiotic performance enhancers

Generic name	Target animal species
Carbadox	Piglets
Olaquindox	Piglets
Roxarsone	Pigs and poultry
Arsenilic acid	Pigs and poultry

With the strict legislation in the EU, since 1999 the listed products can no longer be used in pig and poultry feeding.

. . . market

In Asia, Africa and Latin America, the low-cost products are still popular and they are widely used. Generic products are supplied at low cost by unlicensed manufacturers from India and China.

The global sales turnover was estimated at $55 million in 1999. The market has shrunk by 60% over the past five years.

2.3.2 Probiotics

Probiotics are live microbial organisms, which are orally administered to colonise the digestive tract system. They affect the balance of gut microbials, improving health and performance.

It is generally accepted that the microbial flora of the digestive tract has a considerable effect on the health status and performance of animals. Imbalances of microbial flora may result in colonisation with pathogenic microbes, leading to infections and depression of growth.

Probiotics exhibit a whole range of effects, helping young animals to establish stable flora and to restore the same in old animals after intestinal disturbances. Beneficial effects of probiotics can be summarised as:

- fast colonisation with probiotic organisms
- attaching to the gut epithelium and preventing the attachment and colonisation of pathogenic microbes
- formation of specific defence substances, eg lactic acid
- immuno-stimulation of the gut wall to form additional antibodies
- supporting build up of healthy gut flora after medical treatment
- less formation of bio amines and microbial toxins

Probiotics are intact and alive microorganisms or viable spores from microorganisms, whereas antibiotics are composed of metabolites isolated from microbes. Probiotics are not growth enhancers but they compete with antibiotic growth enhancers in the market. Due to the natural image of probiotics, they are increasingly accepted by consumers and farmers.

The microbial organisms forming probiotics are anaerobes, which colonise the intestinal tract. They include lactic acid forming bacteria, such as *Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei* and *Enterococcus faecium*. All these bacteria adhere to the intestinal wall where they can build thick layers of cells. The release of lactic acid supports living conditions for beneficial bacteria.

A second group of probiotics are the aerobic spore building organisms, which include *Bacillus cereus, Bacillus subtilis* and *Bacillus lichniformis*. These bacteria do not adhere to the intestinal tract, although Bacillus cereus may also grow in an anaerobic environment.

Saccharomyces cerevisiae and *Saccharomyces boulardii* are live yeasts, which are primarily promoted for young animals, particularly piglets and calves. It is claimed other animal species like poultry, dairy cows, pets and horses also benefit from the product. The main applications are for stress relief and inhibition of scouring. In ruminating animals, *S. cerevisiae* is claimed to support degradation of cellulose in feed.

Probiotics have the ability to inhibit the growth and multiplication of pathogenic bacteria in the digestive tract such as *Salmonella spp, Pseudomonas spp, Escherichia coli*, and *Bacillus proteus*. Although several modes of actions are known for probiotics, not all functions are fully understood and trial results are not consistent. Possible reasons of failure are discussed in the literature.

. . . application

The major application of probiotics is in young animals. In piglet and calf feeds they are widely accepted as a feed additive. Pets and horses are another target animal group. Zootechnical parameters that are improved after the addition of probiotics are higher viability, fewer incidences of diarrhoea and better feed conversion. A newly promoted indication of use is the control of micro-flora in liquid pig feed. By adding lactobacilli to the liquid feed, the pH is reduced to a point where the growth of unwanted bacteria are suppressed.

. . . forms and formulations

Commercial probiotic products are offered in the physical form of freeze-dried granules, boluses and pastes. Particular products are also formulated for addition to drinking water.

. . . market

It is difficult to overlook the large number of probiotic products. Inclusion levels and concentrations vary between products. For inter-species comparison, cost of products is expressed as inclusion cost per tonne of feed (see Table 2.78).

Table 2.78: Inter-species comparison of inclusion costs for probiotics, 1999

Animal species	$/tonne of feed
Cattle	4.00–6.00
Calves	4.00–7.00
Sows	2.00–4.00
Piglets	2.00–3.00
Growing pigs	1.00–2.00
Poultry	2.00–3.00

The use of probiotics is regulated by feed legislation in the US as well as in Europe. The Association of American Feed Control Officials (AAFCO) publishes a complete list of permitted probiotic strains and rigorous testing schemes are in place. In the EU, such testing and regulation schemes also exist (Directive 94/114/EU). A complete list of licensed products has only recently been established. National laws however, grant exceptional permission to products awaiting approval which allows restricted use. EU-wide approval is being processed.

Price level for probiotics has steadily decreased over the past few years. With the consolidation of the supply industry and increasing legal requirements for obtaining approval for probiotics, no further fall in price is anticipated and price levels could now stabilise.

The use application of probiotics is most widely established in North America and in Europe. The dominant markets in Europe are in the UK, Scandinavia, France and Germany. In Asia the market is developing slowly. The ban on most antibiotic growth enhancers in the EU has enabled alternative products to emerge. Probiotics are one class of products, which will benefit from recent developments through higher acceptability and broader use. Asia, including Japan is following the trend of replacing feed antibiotics with environmentally acceptable products.

Probiotics are selling at almost $60 million. Based on a conservative estimate this figure will surpass $70 million within five years time (see Table 2.79).

Table 2.79: Global sales of probiotic products, 1995–2000 ($ million)

Region	1995	1999	2004
Europe	7	16	20
Americas	18	23	28
Asia	9	16	21
RoW	1	2	3
Total	35	57	72

Live yeasts accounted for an additional turnover of approximately $95 million in 1999. A 30% growth is anticipated till 2004.

From a consumer perspective, the European market favours the use of probiotics over antibiotics. Probiotics have the potential to fill the gap left by the exclusion of most antibiotic growth enhancers in the EU. The high cost of probiotics will hamper their complete replacement of the antibiotics market. In a market where animal products are traded on a worldwide basis, production costs will govern decisions on non-essential feed additive use.

. . . companies

The concept of probiotics demands high investment in R&D and technical support. Companies involved in the feed additive industry, however, have reduced their expenditure on R&D during the past few years. Manufacturers of probiotics are not generally major international companies. Their financial background is limited and international market exposure often lacking. It is debatable whether probiotics will ever reach the level of market penetration achieved by antibiotics in the past.

The major manufacturers and sales organisations of probiotics are listed in Table 2.80. As some basic producers sell their products through distributors, important marketing and sales organisations are also included in the list.

Table 2.80: Global market shares of probiotic manufacturers and marketers

Manufacturers/marketers	% market share
Agritec Santel– Canada and France	7
Asahi Vet – Japan	7
Bel Industries–France and US	4
Chevita – Germany	3
Chr Hansen – Denmark	15
Far Mor Biochem – US	5
Kemin – US	3
Lallemand – France	14
Medipharm – Sweden	8
Sankyo, Bio-Seiyaku, Eisai – Japan	13
Uniform Cernitin – Switzerland and Sweden	3
Others*	18

*Note: * there numerous producers of probiotics with regional importance*

2.3.3 Prebiotics

Prebiotics substances are poorly or non-digestible food ingredients. They selectively stimulate growth of particular microorganisms in the gut of the host animal. By supporting beneficial gastointestinal bacteria they suppress development of pathogenic or potentially pathogenic microbes.

Chemically speaking, prebiotics are described as non-digestible polysaccharides and oligosaccharides. They occur naturally in feeding stuffs of plant origin and in lower organisms like yeast cells. Between two and ten sugar units form an oligo- or polysaccharide.

It is generally accepted that the colon is populated with a micro-flora that represents a dominant ecosystem. Prebiotics can feed these beneficial colon bacteria such as *Lactobacilli* and *Bifidobacteria*. In doing so, they stabilise the ecosystem by protecting the colon from colonisation with pathogenic bacteria. The following biological functions are claimed for the use of prebiotics:

- Regulation of faecal transit
- Reduced risk of digestive infections
- Better regeneration of intestinal flora
- Improved absorption of minerals and other nutrients

Much research into the effects of prebiotic use is being conducted by the scientific community. Despite many positive and beneficial results, not all of the studies have presented convincing data. In some, no change in micro-flora pattern nor on volatile fatty acids composition could be found. Similarly studies on young pigs showed no difference in growth rate and no change in incidence of diarrhoea.

. . . source

There are a large number of different oligosaccharides. Commercially, there are two predominant groups in the market:

- Fructo-oligosaccharides made either by hydrolysation of inulin or by transfructolysation of sucrose

- Mannan-oligosaccharides derived from yeast cell walls

. . . forms and formulations

Levels of inclusion vary between products and animal species (see Table 2.81). Normal recommended supplementation levels are between 200g and 1,000g per tonne of feed.

Table 2.81: Typical levels of inclusion and cost of prebiotics

Product type	Animal species	Inclusion level (gram/tonne)	Cost ($/tonne of feed)
Fructo-Oligosaccharides	Piglets/growers	200–400	0.40–1.00
	Calves	400	0.80
Mannan-Oligosaccharides	Piglets/growers	500–1000	1.00–3.00
	Poultry	500	1.00

. . . market

The concept of mannan-oligosaccharide was first invented and widely tested in the US and still finds its major markets in the Americas. In contrast the market success of fructo-oligosaccharide began in Europe. Although the overall market for both types of prebiotics is still fairly small, the anticipated market growth is promising.

So far, the main sales areas for prebiotics are Europe and the US. Oligosaccharides are priced at $2.00–$4.00 per kg or from DM 5.00–DM 11.00. Price depends on type of formulation and

degree of purity. Products derived from fermentation processes are generally priced higher. At the time of first introduction of mannan-based oligosaccharides in the early 1990s, prices were in the range of $6.00/kg. Current prices have fallen to $2.00–$4.00 per kg.

It is anticipated that turnover of prebiotics will almost double from $29 million in 1999 to $52 million in 2004 (see Table 2.82). European prices are expected to decrease and the present price gap between the dollar and Euro will be closed. Continuing promotional efforts will increase the market by more than 100% within five years.

Table 2.82: Global sales of prebiotics, 1999 and 2004 ($ million)

Region	1999	2004
Europe	8.0	14.0
Americas	11.0	17.0
Asia	8.0	18.0
RoW	2.0	3.0
Total	29.0	52.0

. . . companies

The number of suppliers of prebiotics is still limited. The additive is marketed in the human food sector as functional food with increasing success. It is anticipated that this will motivate more companies to invest in the development and production of prebiotics. The main manufacturers of oligosaccharides, which sell their products to the feed market, are listed in Table 2.83. Estimation of market share figures is valid for 1999.

Table 2.83: Global feed prebiotics manufacturers, with market share figures

Manufacturer	% market share
Orafti – Belgium	27
Beghin-Say – France	21
Alltech – US	35
Consucra – The Netherlands	5
Borculo Domo – The Netherlands	4
Others	8

2.3.4 Enzymes

Enzymes are highly complex proteins acting as catalysts in chemical reactions in the living cell. They act on specific substrates and accelerate chemical reactions within the metabolism in a particular direction. The chemical reaction changes the molecular structure of the substrates while the catalysts remain unchanged in mass. The amount of enzyme required to act on a given amount of substrate is very small.

Enzymes are present in all living cells of microorganisms, plants and animals. Animals release enzymes into the digestive tract lumen to break down complex food compounds into basic nutrient structures. Digested end products are amino acids and peptides, simple sugars

and fatty acids. The monomer nutrients are then absorbed through the digestive wall into the blood stream and lymphatic system.

In the compound feed industry two types of enzymes are added to practical feed formulations, of which carbohydratases have the widest use application. These are enzymes which act on non-starch-polysaccharides (NSP) or other specific carbohydrates with low digestibility. The other type of enzymes are phytases which act on phytin-bound phosphorus and help to release the phosphorus and enable better absorption.

NSP are substrates that are present in many feeding stuffs. The endogenous enzymes of the host animal digest these substrates poorly. With the addition of the NSP-enzymes, some of the inherent energy of NSP can be unlocked and subsequently used productively. Besides saving valuable energy, several other benficial effects on commercial pig and poultry production are documented.

In cereal grains much of the element phosphorus is bound in the form of phytate, which is a complex phosphorus salt of phytic acid. Phytate-bound phosphorus is poorly absorbed by chicken and pigs as their intestines lack the subtrate specific enzyme phytase. Adding phytase to feed increases the digestibility of this organically bound phosphorus and reduces the amount of inorganic phosphorus that would otherwise need to be added. This in turn reduces the level of inorganic phosphorus in the manure waste stream and consequently the level of water pollution. This is an important environmental benefit, as in several countries phosphate pollution from swine and poultry operations is under increasing regulatory scrutiny. The Netherlands and Denmark already have restrictive legislation in place.

. . . application

The concept of adding exogenous enzymes to feed was developed because not all nutrients present in foods are well digested by endogenous enzymes. The aim is to improve the utilisation of feed-born nutrients, which would otherwise be excreted in their undigested form.

Enzymes are added to compound feed to aid digestibility and increase the amount of substrates available to the animal. Nutrient utilisation is thus improved, resulting in better performance overall. Benefits include improvements in growth rate, feed conversion ratio and egg production.

Carbohydratases and phytases are mostly used in broiler, turkey and pig feeds. Levels of addition vary according to the type of enzyme product and the manufacturer's formulation. In most cases, recommended addition levels for commercial products are 50g–2000g per tonne of feed.

. . . forms and formulations

Like all proteins heat treatment leads to loss of activity in enzymes. As most feeds are processed in pelleting mills at temperatures above 75°C, suppliers advise spraying liquid products onto the pellets. This is particularly important for the more sensitive phytases. Some companies are promoting their products as heat-stable enzyme formulations, however the stabilisation is only relative and not absolute.

. . . market

Commercial enzymes first appeared on the animal nutrition market in the 1980s. Since then several companies have launched enzyme products. The nutritional efficacy of enzymes of the same class cannot be sufficiently compared by chemical analysis. Time consuming and costly feeding trials are still the evaluation method of choice.

The market for feed enzymes in 1999 was estimated at €138 million ($138 million), of which 67% were carbohydratases and 33% phytases.

Within the group of carbohydratases, NSP enzymes are the most important in terms of volume and sales. Another enzyme group is designed for soybean and maize based rations. This group of enzymes accounts in sales turnover for approximately 15% of all carbohydrate enzymes.

The price level for NSP enzymes has fallen constantly over the last 10 years. The inclusion cost per tonne of feed started at above DM 9.00 in the early 1990s. Only 10 years later it is as low as DM 2.10 (see Table 2.84). Inclusion costs of DM 1.50 per tonne of feed were seen in early–mid 2000. Beside a straight price reduction per kg of enzyme product, some companies also reduced their recommended inclusion rate per tonne of feed. This increased cost-competitiveness.

Table 2.84: Inclusion cost of NSP enzymes per tonne of feed, 1990–2000

Year	2000*	1999	1998	1997	1996	1995	1990
DM/tonne of feed	2.10	2.60	2.90	3.30	4.20	4.40	8.40

*Note: * First quarter*

. . . companies

Although there is a seemingly endless number of companies selling NSP enzymes, only a few manufacturing companies dominate the market. In addition, many manufacturers have entered into strategic alliances with established, marketing-oriented organisations.

BASF is marketing and selling the enzymes produced by the Dutch company DSM. Roche is presently selling enzymes from Yakult, Iogene and Novo and has signed a cooperation agreement with Novo that will become effective in January 2001. It is anticipated that some, if not all, enzymes of the Roxazyme line will be discontinued in the near future. With the agreement Roche will become solely responsible for the marketing and sales of the Novo enzyme line. FinnFeeds, the world leader in carbohydratases, merged with Danisco in 1999. They market enzymes from manufacturer Genencor, which again is a joint venture between Eastman Chemical and Danisco.

The major manufacturers and marketers of carbohydratases are given in Table 2.85. The list of marketers takes account of the fact that additional companies have formed alliances with given manufacturers. Lohmann Animal Health of Germany and Orffa of the Netherlands, for example, are marketing Novo enzymes in particular countries in Europe and the Middle East area.

Table 2.85: Market share of manufacturers and marketers of carbohydratases, 1999

Manufacturer/marketer	% market share
Genencor/Finnfeeds*	47
Novo Nordisk/Roche*	26
DSM/BASF	14
Yakult, Iogene /Roche*	7
Others	6

*Note: * Additional distributors market and sell manufacturer's products*

The global market for phytase was worth approximately €46 million in 1999. Average volume growth is estimated at about 25% per annum for the next five years. Average inclusion costs per tonne of feed of around DM 3.50 did not change much until mid 2000. This is explained by the uncompetitive market situation as DSM/BASF are dominating the market (see Table 2.86). The only other significant company in the market is Novo which is marketing its phytase through different local sales organisations. In the third quarter of 2000, phytase inclusion price fell to DM 2.50 per tonne feed. The drastic price decrease is explained by the launch of the new phytase from Novo/Roche. Unlike other phytases the new Bio-Feed Phytase is claimed to be stable throughout feed processing.

Global launches of additional phytase products are anticipated from several other companies. Alltech has already launched a product in Asia. The enzyme is derived from non-recombinant microorganisms. Finnfeeds has a product in its R&D pipeline, but not yet ready for the market. Kyowa Hakko of Japan has released a phytase in the domestic market only.

The main reason for other companies not being able to launch an own product on a global basis is the wide coverage of the phytase patent held by DSM (ex Gist Brocades company). The former Novo Nordisk phytase product has been challenged for patent infringement from DSM by a EUlawsuit. The case is pending in Belgium. The new Bio-Feed Phytase from Novo Nordisk/Roche is said to circumvent the valid DSM patent. After some sales in Taiwan and Korea and its introduction in the US in early 2000, Roche launched the Bio-Feed Phytase in Europe in July 2000.

Table 2.86: Market share of manufacturers and marketers of phytase, 1999

Manufacturer/marketer	% market share
DSM/BASF	69
Novo Nordisk/Roche	29
Others	2

*Note: * marketing and sales through regional distributors*

2.3.5 Feed additives of plant origin

Botanical feed additives are plant stuffs containing particular chemicals, which have beneficial effects in the digestive tract. Phytochemicals of known and unknown origin are synthesised in plants to act as growth regulators, carotenoids (pigment), pest repellents, disease preventives and attractants for insects and birds. The active substances are produced in leaves, fruits, bulbs and roots.

Many suppliers claim a variety of benefits for their products, including disease prevention, immune enhancement and treatment of digestive disorders. When such health claims are made for veterinary products they require regulatory approval. The marketing claims made for botanical feed additives have not been subjected to the same legislation. Research into botanical feed additives is rare and not always convincing. More R&D is required to prove the efficacy of the botanicals as performance and health enhancers. However, although feed botanicals may not provide the best value, their use is not considered harmful to animal health or to humans.

. . . source

Most of the botanical feed additives offered in the market are derived from herbs and spices. These ingredients are claimed to have antimicrobial, antioxidant, immune modulating, growth enhancing and digestive functions. Most feed legislation does not yet regulate the use of botanical additives. The US Food and Drugs Administration (FDA) has listed some botanical substances as generally recognised as safe (GRAS), but many lack specific approval for use in feed. It is not surprising that there is a lack of information on safety and efficacy in animal production for most of the botanical products, given the large variety of plants.

Flavouring substances derived from plant stuffs are considered as a sub-group of botanical feed additives. This type of products is covered under taste and flavour substances (see Section 2.2.3).

Several companies promote their botanical feed additives as the natural alternative to antibiotic growth promoters as there is some evidence that several phytochemicals exhibit antimicrobial property. Garlic is a prominent example as it contains sulphides inhibiting the growth of bacteria and it is promoted in the treatment of diarrhoea of young animals, such as calves and piglets. Similar antimicrobial action is also reported for other phytochemicals such as thyme, pepper, fenugreek, cayenne and basil.

. . . market

Botanical feed additives are sold in a multitude of forms and concentrations. The variety of products means that estimating sales quantities is practically impossible and not worthwhile. Assuming that 90% of all products are used in Europe and North America, the total market is estimated at DM 55 million (see Table 2.87). The single largest product is garlic which accounted for a turnover of DM 13 million in 1999. Spices represent a global turnover of more than DM 9 million.

Table 2.87: Global sales turnover of botanical feed additives (DM million), 1994–2004

Year	1994	1999	2004
DM million	17	55	90

With the gradual retreat of antibiotic growth promoter, the market has opened up for alternative feeding strategies and products. Although botanical products still lack convincing scientific evidence of their effectiveness under practical conditions, the annual market growth is forecast at a two-digit percentage. Since the EU ruling on antibiotic growth enhancers (see

section 2.3.1) there is increasing concern in North America about the risk of creating drug-resistant pathogenic bacteria. This will create a worldwide niche market that will foster the sales of botanicals.

The global market potential is enormous. A turnover of several hundred million German Marks could be achieved in 5–10 years, provided R&D is able to provide sound evidence that botanicals can effectively replace feed antibiotics.

. . . companies

Basic producers, traders of botanicals, formulation businesses and sales organisations are very often owned by other companies, making a breakdown of the botanical feed additive market by company difficult to assess. Additionally, several botanicals are only of local importance and they are not marketed elsewhere.

There are hardly any global players in the botanical feed additive market. Significant companies with international sales activities are listed in alphabetical order in Table 2.88.

Table 2.88: Companies involved in marketing and sales of botanical feed additives

Biomin GTI – Austria
CRINA – Switzerland
Delacon Biotechnik – Germany
Den Lokale Handel – Denmark
Desert King – US
Indian Herbs – India
Micro-Plus Konzentrate GmbH – Germany
NorFeed – Denmark
Pancosma – Switzerland

2.4 Disease preventing agents

Several drugs are routinely added to feed to prevent disease outbreaks caused by protozoal microbes. The drugs are permitted as feed additives and require no prescription. They are provided as prophylactics against disease-causing coccidia and histomonals.

2.4.1 Anticoccidials

Anticoccidials are added to feed to counteract infection of the intestinal tract by different *Emeria* species belonging to the class of protozoa. Different species damage different places in the intestinal wall and one of them may cause serious bleeding.

All farm animals can be affected by coccidial infections. It causes significant losses in poultry, frequently causing growth depression, impaired feed conversion and, ultimately, high mortality, unless anticoccidials are supplied as a preventive measure. Coccidiosis is a disease, which is typically found in intensive production systems where animals are crowded in large numbers. In pigs, sheep and cattle coccidian infections can also cause depression of performance.

. . . source

Anticoccidials are drug agents produced from chemical synthesis or by fermentation process.

. . . application

Growing birds are generally supplemented with anticoccidials. Laying birds are fed the anti-protozoan drug only in case of severe disease outbreak. Eggs, however, must then be discarded.

. . . forms and formulations

There are two groups of anticoccidials, coccidiostats which prevent the development of coccidia and coccidiocides which kill coccidia.

The distinction is academic, as both drugs can effectively prevent the outbreak of the disease coccidiosis, but an effective anticoccidial programme must take into account their different modes of action. The efficacy of single products (shuttle products) can be optimised by applying a well-balanced sequence of products which can prolong the effective lifetime for individual drugs. This is important as there are few new anticoccidial entering the market.

Feed conversion ratio (FCR) has improved substantially for intensively reared broilers from 2.5kg in 1985 to less than 1.8 kg in 1999. The grow-out period for a 2 kg broiler was reduced at the same time from 56 days to about 40 days. Anticoccidal concentrations in feed were generally constant throughout this time. In effect, drug use per adult bird declined.

The major anticoccidial products are listed in Table 2.89, with their generic name and brand name. The addition levels to feed vary considerably according to local law, global region, the threat of coccidiosis and feeding practice. Customised combinations are only included where a significant penetration of the market is given.

Table 2.89: Manufacturers of anticoccidials for broilers, with generic names and trademarks

Manufacturer	Generic name	Trademark
MSD	Aprinocid	Amprocox, Arpocox
MSD	Amprolium*	Amprol
MSD	Amprolium+Ethopabate	AmprolPlus
Merial*	Clopidol*	Coyden
Merial	Clopidol+Methylbezoquate	Lerbek
Alpharma	Decoquinate*	Deccox
Janssen	Diclazuril	Clinacox
Alpharma*	Zoalene*	DOT
Intervet/Hoechst	Halofuginone*	Stenorol
Alpharma/Roche	Lasalocid	Avatec
Alpharma/Roche*	Maduramicin*	Cygro
Elanco*	Monensin*	Elancoban
Elanco	Narasin	Monteban
Koffolk	Nicarbazin	Nicarb
Elanco	Nicarbazin+Narasin	Maxiban
Alpharma/Roche	Robenidine*	Cycostat

. . . continued

Table 2.89: (continued)

Manufacturer	Generic name	Trademark
Intervet/Hoechst	Salinomycin*	Sacox, Biocox
Koffolk/Pfizer	Semduramicin	Aviax
Alpharma/Roche	Sulfadimethoxin+	
Ormetoprim	Rofenaid	125+75

*Note: * Several manufacturers and trademarks*

... market

The main factors which determine the volume market for anticoccidials are:

- The number of birds raised
- The ratio by which feed is converted into body mass (feed conversion ratio)
- The penetration of the market with anticoccidial drugs

Between 1985 and 1999 global poultry meat production has increased by approximately 8% per annum. While the use of anticoccidials in Europe and North America is common practice, there are still many places in Asia, Africa and Latin America where the drugs are not applied as a disease preventive on a routine basis. Nevertheless, the penetration of feed that contains anticoccidials has improved in the past years.

The patent expiration of most of the anticoccidial drugs has initiated a widespread production of generic products. They contain the same active substance as the original branded drug. Therefore they are, by and large, interchangeable with the original branded drugs. Differences can be found in the galenic formulation and, in some cases, in the purity of the drug.

Salinomycin is a good example with regard to quality differences between original and generic drugs. Several companies in China and in Eastern Europe produce the anticoccidial. When generic salinomycin entered the European market, the chemical analysis revealed a contaminant known as elainophylin. This side product was repeatedly reported in various batches of generic salinomycin. Elainophylin is suspected to cause mucosal inflammations and performance depressions. The publication of the analytical results led to a complete withdrawal of generic salinomycin from the EUmarket.

Prices for generic anticoccidials vary considerably. Important price determining factors include:

- Competition from other generic products
- Differences in recommended inclusion rates
- Target animal
- Importation tax

The product cost per kg is not the best way to compare anticoccidials, as the effective dose varies between 1 ppm for diclazuril to 125 ppm for nicarbazin. In addition, the concentration of the ai differs from one product formulation to the next. The same generic anticoccidials are also sold at different concentrations. The ideal cost comparison is obtained by expressing the cost of the drug per tonne of complete feed.

The inclusion cost for anticoccidials varied between $1.45 to $4.70 per tonne of feed in 1996. The products at the lower end of the price range are generally chemical anticoccidials and generic ionophore anticoccidials from Chinese manufacturers. At the top end of the price scale are Roche's branded anticoccidials. Up to 1999, price levels decreased by approximately 15% since 1997.

Salinomycin and monensin have captured the largest part of the global anticoccidial market with more than 50% (see Table 2.90), with lasalocid and maduramicin following next, the four ionophores cover more than 75% of anticoccidial sales.

Table 2.90: Global market shares of anticoccidial feed additives, 1999

Generic name	Manufacturers*	% market share
Diclazuril	Janssen	3
Lasalocid	Alpharma/Roche	14
Maduramicin	Alpharma/Roche – China	11
Monensin	Elanco, Pharmachim – Bulgaria	22
Narasin	Elanco	5
Nicarbazin	Koffolk	5
Nicarbazin/Narasin	Elanco	3
Robenidine	Alpharma/Roche – China	2
Salinomycin	Intervet, Kaken, Mitsui, Alpharma/Roche, Intervet/Hoechst, Koffolk/Pfizer – China	29
Others		6

*Note: * Different manufacturers are divided by comma*

The total market for anticoccidials was worth $480 mllion in 1999. On a global basis, the quantitative use of anticoccidial drugs has grown at 4–6% per annum since 1985. Sales development in 1998 showed a downturn due to the economic crisis in Asia. With the consolidation and concentration of the medicinal feed industry in 1999 and 2000 it is difficult to predict the development of prices. Projections for the next five years reveal a continuing downtrend in inclusion cost. Global sales volume will grow at about 3% per annum. Sales value till 2004 will stabilise around the 1999 figure. Vaccination of layers and broilers may become a viable alternative if the cost/efficacy ratio of the vaccines proves better than that of anticoccidial drugs.

2.4.2 Antihistomonals

Histomoniasis or blackhead disease is a parasitic disease affecting the caeca and liver of many gallinaceous birds. The most severe infectious damage is caused in turkeys. Antihistomonals are synthetic drugs that are added to feeds as a preventive. They can control outbreaks of the disease.

. . . forms and formulations

There are several drugs of the nitromedazole group and nitrofuran group, which are active against the histomoniasis causing protozoa. All products have a broad antibacterial and antiprotozoal spectrum. Therefore, their general use is not limited to acting as a preventive for histomoniasis.

. . . market

The inclusion costs for antihistomonals vary between $0.65 to $2.50 per tonne of feed. Dramatic price changes are not anticipated. Low-cost products are generally offered from China. The global market is estimated at above $5 million in 1999. An average annual growth rate of 2–3% is projected till 2004.

. . . companies

There are four main products in the market, all listed in Table 2.91. The major feed additive suppliers Roche, BASF and the former company Rhône-Poulenc were manufacturers and suppliers of antihistomonals. All terminated production because of patent expiration, low profitability and increasing competition from Chinese manufacturers.

Table 2.91: Antihistomonals manufacturers and marketers with generic and brand names

Manufacturers/marketers	Generic name	Trade name	Dosage mg/kg feed
Merial, Micro Biologicals BASF – China	Dimetridazole*	Emtryl/Lutrizol/ Dazole	100–200
China	Ipronidazole*		50–85
Duphar, Solvay, Fort, Dodge, American Home, Salsbury Lab, Duphar	Nifursol*	Sulfuuride/Salforit	50–75
SKB – China	Furazolidone*		110
Alpharma	Nitarsone	Histostat	187

*Note: * Several manufacturers and trademarks*

CHAPTER 3
COMPANY PROFILES

This section analyses the top 10 companies that produce and market feed additives. Three additional companies are profiled that are anticipated to enter the top 10 in the year 2000. This may be either by acquisition of the entire business segment, by adding products to another league member or by take-over of an entire company.

Alpharma is already in the top 10. With the purchase of Roche's medicinal feed additives (MFAs) it will climb up to about fifth place. Although Roche will lose turnover of $215 million from 1999 for its MFA sales, the vitamin giant maintained its prominent number one position in 2000.

Hoechst Roussel Vet was fully incorporated into Akzo Nobel/Intervet in the year 2000. With the addition of the feed additives marketed by several divisions of Akzo Nobel, the 1999 sales of Hoechst will have been exceeded.

The sale of Pfizer's feed additives production to Koffolk's owners Philipp Brothers Chemicals was announced in October 2000. The Israel-based Koffolk may now enter the top 10.

The company profiles are divided into four main areas. The first includes the address, contact details, and key personnel within the company and gives background information about the company, including company history, business strategies, subsidiary companies and general financial status. The next section is dedicated to the feed additive business itself with product portfolio, R&D strategy, sales turnover and additional market information.

The third section summarises the major company activities throughout the past 10 years, in relation to the feed additive business. Finally an outlook is given for potential acquisition and merger candidates.

3.1 Hoffmann-La Roche

Vitamin and Fine Chemical Division
CH-4070 Basel
Switzerland

Tel: + 41 61 6881111
Fax: + 41 61 6873242
Website: www.roche.com
E-mail: markus.altwegg@roche.com
Markus Altweg: Head of Vitamin and Fine Chemical Division

Hoffmann-La Roche was founded in 1896 in Basel, Switzerland. It is a research based healthcare group of companies. The major business activity sectors include pharmaceuticals, diagnostics, flavour and fragrances, and vitamins and fine chemicals. According to the company's vision, the activities focus on the prevention, diagnosis, monitoring and treatment of diseases and on the promotion of general wellbeing.

The group turnover in 1999 reached SwF 27.6 billion, of which the pharmaceutical division made up 60%; the vitamin and fine chemical division has fallen back to SwF 3.65 billion which is equivalent to 13%.

The vitamin and fine chemical division markets and sells its products to the industry's feed, food, pharmaceutical and cosmetic sectors. The feed industry is the most important in terms of turnover at approximately 57%. The focus is clearly given to products that are added to feed. This includes nutritionals, colouring products (carotenoids) and enzymes. The medicinal feed additive portfolio was sold to Alpharma in 2000.

3.1.1 Feed additive business:

This wide product portfolio covers the following groups:

- Vitamins – basic manufacturer of all vitamins except vitamin B_{12}, K_3 and niacin
- Carotenoids – basic manufacturer of astaxanthin, canthaxanthin, apo-ester, betacarotene
- Organic acids – citric acid
- Enzymes – strategic alliance with several manufacturers

R&D activities are restricted to a few product groups, ie carotenoids, medicinal feed additives and enzymes. In-house research is located in France at the Animal Nutrition Research Center in Village-Neuf and in the US at the Biotechnology Research Centre in New Jersey, US.

Traditionally, market share figures for the group of vitamins were in the range of 55%. In the last 10 years it steadily dropped to slightly above 40%. In 1999 the US and other state authorities sued the major vitamin manufacturers, including Hoffmann-La Roche, for illegal price fixing. As a consequence, prices for most vitamins have fallen. This development will influence market share positioning of all major suppliers in the market.

Hoffman La-Roche is present in all major markets through more than 70 subsidiaries. Its market presence is equally strong around the world. In small markets it sells through independent agencies. The breakdown of turnover according to continents is as follows:

Americas – 40%
Europe and Africa – 45%
Asia and Oceania – 15%

3.1.2 Corporate and product activities

- A new vitamin B_2 plant in Grenzach,Germany is to replace older facilities on the same site and in Fukuroi, Japan towards end of 2000

- Also vitamin B_1 and biotin plants are to be enlarged on the Grenzach site by end of 2000; the plant is to replace the US site at New Jersey and Village-Neuf production facilities in France

- A strategic alliance between Novo Nordisk and Roche is to become effective by January 2001. As part of a joint development, Roche introduced a new phytase product in 2000

- Roche is to withdraw from the MFA business in 2000 and has sold its MFA portfolio to Alpharma for approximately $300 million. Roche had attained a MFA sales turnover in 1999 of about $215 million

- Roche pleaded guilty to illegal price fixing of vitamin and carotenoids in the US, EUand other countries in 1999. The conspiracy forced customers to pay artificially high prices

- Roche established several ventures with Chinese companies for the production of vitamins A and E and citric acid in 1996 and 1997

3.1.3 Prospects for future mergers and acquisitions

The vitamin and fine chemicals division may be spun-off as an independent group. This move is likely to follow the same procedure as Roche's flavour and fragrance division which was spun off under the name of Givaudan-Roure June 2000.

As Roche develops into a pure pharmaceutical company a sell off of the vitamin and fine chemicals division is probable. Acquisition candidates are scarce due to the size and profitability of the business. Potential candidates could be ADM or Nestle.

3.2 BASF Aktiengesellschaft

D-67056 Ludwigshafen
Germany

Tel: + 49 621 6049393
Fax: + 49 621 6041886
Website: www.basf.de
E-mail: stefan.borgas@basf-ag.de
Stefan Borgas, Director: Global Marketing Animal Nutrition

BASF (Badische Anilin-und Sodafabrik) was founded in 1865 as a dyestuff and chemical company. Today, BASF is one of the worlds leading chemical companies. With over 100,000 employees and operation facilities in about 40 countries they generate a group turnover of €29,500 million. The main business divisions cover plastics and fibres, chemicals, health and nutrition products, colorants and finishing products, and oil and gases.

Within the health and nutrition product division, the main activity in the animal nutrition field is in the fields of vitamins, carotenoids, accessory feed additives, organic acids, minerals and amino acid.

Fine chemicals are marketed and sold to the industry's feed, food, pharma and cosmetic sectors. BASF is particularly strong in the feed industry, which makes up approximately 65% of its turnover. Vitamins and carotenoids create the majority of sales. In this sector BASF's philosophy is to copy and follow strategies of the market leader Roche.

3.2.1 Feed additive business

This product portfolio covers:

- Vitamins – basic manufacturer of vitamins A, E, C, B2, calpan, betacarotene
- Carotenoids – basic manufacturer of canthaxanthin, apo-ester, citranaxanthin, astaxanthin
- Organic acids – propionate and formate
- Amino acid – lysine
- Enzymes – NSP enzymes and phytase manufactured by DSM (Gist Brocades)

R&D activities concentrate on new business interest. They include all products characterised as non-commodities, such as carotenoids, enzymes and products from biotechnology. BASF's in-house research station, Forschungsstation Ernährung, is in Offenbach, Germany.

BASF was among the leading vitamin manufacturers that pleaded guilty to illegal price fixing for vitamins, vitamin blends and carotenoids. The US federal court reached a settlement in September 1999, with BASF ordered to pay a fine of $225 million. Some of the companies that fell victim to the price fixing have opted out of the settlement and will pursue state action with the aim of recovering more money. Similar trials are being conducted in the EU and in other countries.

The BASF group products are available in around 170 countries. The global market presence and distribution logistics are exceptionally good, due to the size of the company and the variety of products. BASF animal nutrition products are therefore well known around the world.

The turnover in the fine chemical business reached €770 million in 1999, all derived from the animal nutrition and health sector. The geographical split of BASF's animal nutrition and health sales is estimated as follows:

Americas - 37%
Europe and Africa - 47%
Asia and Oceania - 16%

3.2.2 Corporate and product activities

- BASF and Takeda agreed in July 2000 to unite their vitamin businesses under BASF's responsibility
- Joint venture production plant with Merck and Cerestar for ketogulonic acid (precursor for vitamin C) set up in 1999
- Acquired global lysine business including the production facilities of Korean company Daesang in 1998
- Feed phosphate business sold to Kemira Kemi AB, Sweden in 1998

- Expansion of vitamin B_2 and carotenoid plant in Ludwigshafen in 1997

3.2.3 Prospects for future merger and acquisitions

The acquisition of Takeda's vitamin business has strengthened production of B-group vitamins.

The company is to prioritise consolidation of the joint vitamin businesses of BASF and Takeda in order to reach satisfactory profit margins.

3.3 Aventis Animal Nutrition

42 Avenue Aristide Briand
PO Box 100
F-92164 Antony Cedex
France

Tel: + 33 1 46747000
Fax: + 33 1 40969696
Website: www.aventis.com
E-mail: Barry.Coates@aventis.com
Barry Coates, Marketing and Sales Manager

The merger of Hoechst AG and Rhône-Poulenc SA formed Aventis in December 1999. The new company employs 95,000 people and generated a joint sales turnover of €20,500 million in 1999. The business is focused on the two main activities, pharmaceuticals and agriculture. The new headquarters are based in Strasbourg.

The rationale behind the merger was to create a leading multinational life science company. The company would be better positioned in the global market for sustainable growth with a robust product pipeline and the power of joint R&D for new developments.

The mega-merger combines a joint turnover of €20,452 million for the whole of Aventis. With 72% of total sales, Aventis is a pharmaceutical focused company. On the agriculture side, Aventis is involved in three main areas:

- The veterinary business is covered by Merial a 50:50 joint venture between the former Rhône-Poulenc and Merck

- The crop protection business of Rhône-Poulenc was combined with Agrevo, the former Hoechst and Schering joint venture and incorporated into Aventis

- The ex-Rhône-Poulenc feed additive business was transferred to Aventis Animal Nutrition

The Hoechst-owned animal health company, Hoechst Roussel Vet, was divested for €665 million to the Dutch company Akzo Nobel.

Aventis Animal Nutrition publicly confirmed in May 2000 that it is no longer considered as core business within Aventis. The search is on for a new principal shareholder. The streamlining of the product range makes the acquisition of interest to any feed additive

company in the world. The company has focused on the product groups amino acids, vitamins and enzymes.

3.3.1 Feed additive business

The product portfolio comprises of:

- Vitamins – basic manufacturer of vitamins A, E, and B_{12}
- Amino acids – basic manufacturer of liquid and dry methionine
- Enzymes – basic manufacturer of NSP enzymes

The R&D activities are concentrated on new product formulations, manufacturing methods and new enzymes. In 1999, Rhône-Poulenc entered into a collaboration with the San Diego-based biotechnology company Diversa Corporation to develop novel enzymes.

The sales of all nutritionals accounted for €551 million in 1999. This also includes sales from premixing activities. The revenues from the amino acid reached about 58% of the divisional turnover. Vitamins accounted for 41% and enzymes share is estimate below 1%.

In volume sales of vitamin B_{12}, Aventis is the undisputed market leader. In the production of vitamins A and E, they rank third or fourth among the worlds largest producers. Despite a sales increase in volume terms in 1999, Aventis suffered heavily from falling prices in vitamins and amino acids.

Aventis has a strong position with its feed additives in Europe, but is relatively weak in North America. The global business is managed from four regional offices:

- Paris, France – Europe, Middle East, Africa, CIS
- Alpharetta, Georgia, US – North America
- Sao Paulo, Brazil – Latin America
- Singapore, Singapore – Asia-Pacific Region

The former Rhône-Poulenc was the first company to form joint ventures for the production of methionine in China and in the Ukraine. In Eastern Europe, Aventis holds a prominent position, despite sluggish market development. The breakdown of sales by regions are reported as follows:

Americas – 37%
Europe, Middle East and Africa – 45%
Asia-Pacific – 19%

3.3.2 Corporate and product activities

- Announcement made in May 2000 that the feed additive business should no longer be part of the core strategy. Aventis is looking for a new principal shareholder

- Aventis is to gradually increase the capacity of its Commentry plant in France by 50%. Project began in 2000 and is to be completed in 2002

- Merger of Hoechst AG and Rhône-Poulenc S.A. to form Aventis in December 1999

- Collaboration on development of novel enzymes with biotechnology company Diversa Corp. of San Diego/US in 1999

- In April 1999 Rhône-Poulenc announced it had doubled production capacity at the liquid methionine plant in Burgos, Spain

- Rhodia Nutricao Animal, a subsidiary of Rhône-Poulenc closed down its production plant for liquid methionine in Brazil in 1998

- Rhône-Poulenc sold its Deccox business to Alpharma in 1997

- Joint venture company established between Tianjin Bohai Chemical Industrial Group and Rhône-Poulenc Animal Nutrition for the production of methionine in 1997. Investment of Yuan 700 million was agreed

3.3.3 Prospects for future mergers and acquisitions

With the announcement in May 2000 of the search for a new shareholder for the animal nutrition business, the race is on for a new principal. In view of the size of the business and the product portfolio, Degussa and ADM are seen as the potential candidates. Degussa has a great interest in developing its line of vitamins. The authorities however, may block the acquisition of the methionine business. ADM knows the ex-Rhône-Poulenc business very well from several global feed ventures back in 1996. Aventis' methionine and vitamins would complement ADM's product profile making them one of the top companies in the feed additive business.

3.4 Mitsui Group/Novus

Mitsui Group
2-1, Ohtemachi 1-chome Chiyoda-ku,
Tokyo 100-0004
Japan

Tel: + 81 3 32851111

Novus International Incorporated
530 Maryville Centre Drive
MO 63141 St. Louis
USA

Tel: +1 314 5768886
Fax: + 1 314 5762148
Website: novusint.com
E-mail: msfitz@novusint.com
L E Hooks, President and Chief Executive Officer

The original Mitsui company was founded in 1876, but was dissolved into more than 200 companies in 1947 under the orders of the allied occupation forces to dismantle Japan's industrial conglomerates. One of these companies, Daiichi Bussan, was destined to become the core of today's Mitsui, which was founded when most of the companies dissolved after

the war merged again in 1959. Today, Mitsui is a global trading company with almost 900 subsidiaries and associated offices around the world. Sales revenues accounted for $128,162 million for the fiscal year ending March 2000.

Novus International Incorporated became a member of the Mitsui group, when Mitsui and Nippon Soda acquired the feed additive division of Monsanto in 1991. Mitsui is the major partner, holding 70% of the shares. Based in St. Louis, Novus is solely a feed additive company. It is one of the three giant methionine producers in the world market supplying around 31% of the global demand. Production started in 1984 with extraordinarily high annual growth rates 1993. Thereafter, an annual average growth of 5% was achieved, which is well above most other feed additives.

3.4.1 Feed additive business

The product portfolio comprises of

- Amino acids –MHA
- Antioxidants – ethoxiquin
- Hatchling supplements

Novus is particularly strong in the markets of the Americas and Asia-Pacific. Its Position in Europe is weak. Sales in 1999 were below $500 million. The bulk of sales are related to MHA, which makes up more than 70% of Novus' turnover. The second main product is ethoxiquin for which Novus became the sole distributor. The antioxidant is produced by Monsanto and sold under the brand name Santoquin.

Novus has a presence in approximately 70 different countries, either directly or through distributors. It pioneered the application of liquid feed additives for which it has gained an excellent reputation. The geographical split of Novus sales is estimated as follows:

Americas – 70%
Europe and Africa – 10%
Asia and Oceania – 20%

The success of the application of liquid additives developed in the Americas could never be replicated in Europe. In relation to the size of animal production in Europe, the sales of Novus products are relatively small.

R&D activities are wide-spread and cover areas from feed preservatives, neonatal hatchling supplements, antimicrobial systems for use in food processing, to automated inventory management systems for stored liquids

3.4.2 Corporate and product activities

- 102,000 tonnes capacity expansion for MHA at its Chocolate Bayou facility completed in early 1999
- Agrado – a new feed preservative ingredient for the beef cattle industry launched by Novus in 1998

- The Omnus company for the development of computerised decision enhancing systems for the animal industry founded by Novus in 1995

- Novus expanded its plant in 1994 by 30%

3.4.3 Prospects for future mergers and acquisitions

The expansion projects of Degussa and Aventis will keep pressure on methionine prices. Extension of its product range with other amino acids would help Novus in obtaining a critical mass of products. Ajinomoto's amino acid line would ideally complement Novus.

Novus is a research-based company focusing on its own developments. New innovative products are required to extend its range.

The traditional good relationship with Monsanto suggests further activity in the field of new antioxidants.

3.5 Eli Lilly and Company/Elanco Animal Health

Elanco Animal Health (International)
Four Parkwood-Drop
Code 6823
500 East 96th Street
125 Indianapolis
Indiana 46240
USA

Tel: + 1 317 276 2624
Fax: +1 317 277 7048
Website: www.elanco.com
E-mail: elanco@elanco.com

Eli Lilly and Company was originally founded in 1876 in Indianapolis. Until the end of the 1950s Eli Lilly's business was concentrated in the pharmaceutical area. In 1960 a new division, Elanco, was formed representing the agricultural product line. This first business diversification was followed by expansion into other areas such as the cosmetic industry. Following a decision in 1987 to refocus the business, the animal health concerns were finally concentrated into a new division named Elanco Animal Health.

Eli Lilly generated a sales turnover in the region of $10,000 million in 1999 with around 31,000 employees Sales had grown steadily from a turnover of $5,700 million in 1994, with Elanco Animal Health sales accounting for around 6%. Profit margins from the animal health business are small compared with pharmaceutical products.

Elanco Animal Health offers products for the veterinary and MFA sectors. Veterinary products are parasiticides, food safety products and therapeutic antibacterials. MFAs include anticoccidials and performance enhancers. Elanco employs approximately 2,000 people and has a consistently strong and developed presence in more than 100 markets worldwide.

3.5.1 Feed additive business

Elanco's product portfolio comprises of:

- Anticoccidials – monensin, narasin and combination products (narasin and nicarbazin)
- Performance enhancers – monensin, tylosin, avilamycin

R&D activities are steered by the Greenfield Laboratories in the US at Greenfield, Indiana. Here, livestock research is conducted and research activities elsewhere are coordinated. Current research work is focused on market approvals and on meeting additional regulatory requirements. In the absence of promising new products, Elanco appears to be concentrating its efforts in maintaining the present portfolio of products.

Although tylosin and monensin are offered as generic products, Elanco Animal Health still leads the market for these two MFAs. For avilamycin it holds an increasingly strong position. The product line is highly dependent on antibiotic growth enhancers. Elanco was not directly affected by the 1999 ban of most feed antibiotics by the EU. Due to the strong basis for animal health products in the US and in other parts of the world, the total animal health business could increase by almost 10% from 1998 to 1999.

Sales revenues grew in 1999 to approximately $600 million, of which feed additives accounts for around 70%.

3.5.2 Prospects for future merger and acquisitions

Elanco Animal Health business is well focused on MFAs and veterinary products. The division is the right size to be able to complement its product portfolio by acquisition of smaller or larger companies. Eli Lilly may spin-off the division to concentrate its core activities in a pure life science.

3.6 Degussa-Hüls AG

Feed Additive Division
Weissfrauenstrasse 9,
60287 Frankfurt am Main
Germany

Tel: + 49 069 218 3368
Fax: + 49 069 218 2023
Website: degussa-huels.de
E-mail: feed.additives@degussa-huels.de
Dr Hubert Wenemer, Director of feed additive division (Geschäftsbereich Futtermitteladditive)

Degussa originated as the precious metal refinery of Friedrich Ernst Rössler in Frankfurt. The business was taken over by his sons Hector and Heinrich Rössler, who floated the company in January 1873 to gain capital. In addition to the refining and processing activities, the company entered into the production of chemicals required by the mining industry. One of these – cyanide – which is used for the leaching of gold ore, became more important when

Werner Schwarze succeeded in synthesising methionine from hydrocyanide acid and other chemical intermediates.

Degussa also produces a wide range of precipitated silicas and silicates. They are used as flow aids and absorbents in hygroscopic material, such as spray-dried vitamins or other poorly flowing feed ingredients.

In July 2000 the company merged with SKW, Trotsberg to become Degussa AG. The new headquarters are located in Düsseldorf. The giant energy company Eon AG, which is in turn the result of a recent merger between VEBA and VIAG will hold a 64% share in Degussa. Main activities of SKW Trotsberg are in production of feed and food additives, fine chemicals, construction chemicals, cosmetic chemicals, special plastics, colours and rubber additives.

Degussa's corporate sales fell from €10,593 million in the fiscal year 1997/1998 (September till September) to €9,998 million in the following year. The four divisions; health and nutrition, special chemicals, polymers and intermediates and performance materials, are each responsible for between €2,000–€3,200 million. Revenue of €532 million was recorded for the remaining services division.

Within the health and nutrition division, the feed additive business accounted for €350 million in 1998/1999. This fell by 13% from the previous year. The price decrease on the global market for methionine, is mainly responsible for the drastic fall in sales turnover as it is by far the most important product for Degussa.

3.6.1 Feed additive business

The product portfolio covers:

- Amino acids – basic producer for methionine, lysine and threonine
- Vitamins – basic producer of niacin, formulation of vitamin E
- Organic acid – formate
- Silicas

Degussa is strongly committed to R&D. With 40 employees in technical services and an additional 60 employees in basic and applied research, the company is one of the few still investing in new developments. Recently they concluded work on the chemical synthesis of vitamin E. R&D work for B group vitamins is being piloted. Activities in gene technology will help to optimise fermentation yield for production of amino acids.

Production plants for methionine are located in Wesseling, Germany, Antwerp, Belgium and Mobile in the US. A joint venture agreement for the production of lysine was signed with Cargill to form Midwest Lysine LLC in Blair, Nebraska, US. The plant is adjacent to Cargill's corn wet milling complex. Cargill supplies corn derived raw material and infrastructure services. Production commenced in 2000. The capacity of the plant is about 75,000 tonnes of Biolys 60% product. The production capacity for threonine, which is manufactured by Fermas in the Republic of Slovakia, was more than doubled to approximately 5,000 tonnes per annum.

The sales revenues from feed additive decreased from previous year by 13% to €350 million. Sales figures refer to the financial year from September 1998 to September 1999. The slump

in sales turnover, despite a volume increase, is explained by significantly lower prices for methionine. Methionine is responsible for approximately 80% of Degussa's total feed additive revenue.

3.6.2 Corporate and product activities

- Degussa-Hüls and SKW Trostberg agreed on a merger contract in October 2000, retroactively from July 2000. The two companies transferred their assets to the new Degussa AG headquarters in Düsseldorf
- Subsidiary trading company Neuber GmbH was sold at the end of 2000
- Enzyme manufacturer Röhm Enzmye GmbH sold to Associated British Foods at the end of 1999
- Joint venture agreement with US company Cargill formed Midwest Lysine LLC. in Blair, Nebraska to produce lysine. Production commenced in 2000
- Degussa and Hüls announce merger on March 1998. Merger effective in February 1999
- Degussa acquired rest of the Fermas shares from Biotika at the end of 1998
- Degussa's 40% stake in Finnfeeds International Ltd (FFI) transferred, in full, to Cultor Corporation for £10.8 million in 1998

3.6.3 Prospects for future merger and acquisitions

Degussa has a solid and broad base of products. The dominance of methionine in sales turnover requires future expansion of its product portfolio to reduce dependence on methionine price fluctuation. The vitamin and enzyme business of Aventis would complement the Degussa feed additive portfolio. However a take-over of Aventis' methionine business is unlikely to be accepted by monopoly commissions in the US and the European Union.

3.7 Pfizer Incorporated

235 East 42nd Street
New York
NY 10017-5755
USA

Tel: +1 212-573 2323
Website: www.pfizer.com
E-mail: pedro.lichtinger@pfizer.com
Pedro Lichtinger, CEO and President of Animal Health Group

Pfizer's foundation by two German emigrants goes back to 1849. The business originated in the fermentation and supply of bulk and intermediate chemicals. In 1944 Pfizer's shares were first traded at the New York Stock Exchange. Soon afterwards, it became the world's largest supplier of penicillin. During the last decade Pfizer streamlined its product portfolio to

become a focused supplier of pharmaceuticals and consumer products. The acquisition of the Warner-Lambert company will strengthen its position in the global pharmaceutical market.

The Pfizer group achieved sales revenue of $16,204 million in 1999, of which the animal health sector represents a share of 8%. Despite a growing company turnover the animal health business within the company fell by 12% in 1997 to 10% in 1998 and to 8% in 1999.

Sectors covered are veterinary products and an impressive range of MFAs. Sales revenues from the veterinary products however, outperform MFAs.

Today Pfizer's strategy is clearly focused on the human market. With the acquisition of Warner-Lambert the animal health group no longer represents the core business. In 1999, the animal health group was offered for take-over and aquired by Koffolk, a subsidiary of Philipp Brothers Chemical in April 2000. Whether this includes only Pfizer's MFA product line or more, was not revealed.

3.7.1 Feed additive business

Pfizer's MFA product line comprises of :

- Performance enhancers – tetracyclines, virginiamycin, carbadox
- Anticoccidials – salinomycin, semduramycin, sulfadimethoxine and ormetoprim

Pfizer holds a strong position for its anticoccidials in the Asia-Pacific region and in Latin America. Virginiamycin, a commonly used performance enhancer has suffered since the decision by the EU to ban certain antibiotic feed additives from June 1999.

The MFA product line was estimated to have had a turnover of $360 million in 1999. This equals a 27% share of the sales revenue for the animal health group.

Regional sales split for MFA products is estimated as follows:

Americas – 67%
Europe and Africa – 10%
Asia and Oceania – 23%

3.7.2 Corporate and product activities

- Sales of animal health group products to Israeli based company Koffolk

- Pfizer initiated a legal case against the EU decision to ban the use of virginiamycin as a feed additive

3.8 ADM

Decatur
IL 62525
PO Box 1470
USA

Tel: +1 217 4240 5200
Fax: +1 217 362 8067
Website: www.admworld.com
Email: Allen@admworld.com
G.Allen Andreas, Chariman

The origins of ADM date back to mid 1800 when John Daniels and George Archer began their career as linseed crushers. With the acquisition of a competitive linseed company in 1923, Archer Daniels Midland was created and developed into one of the world's largest corn wet milling and soy processing companies. Although sales in 1999 exceeded $14,000 million this was a decrease of almost $2,000 million from the previous year.

Within a network of over 205 domestic and internationally based plants, eleven cereal grains and oilseeds are processed into a multitude of products used for food, beverage, nutraceuticals, industrial, and animal feed markets worldwide. ADM's four main operations are oilseed products, corn products, wheat and other products and services that comprise of a major transportation network.

ADM's importance in the feed industry results from its large fermentation enterprise. The corporate philosophy combines the advantages of lean management, low overhead costs, a strong position in fermentable substrate supply and fermentation expertise. The feed additive product line is focused on the amino acids lysine, threonine, and a tryptophan-lysine blend called Tryptosine. They also offer vitamin premixes for feed millers. Although ADM also offers natural vitamin E and organic acids, very little is used in the feed industry.

The pig feed manufacturers are the major user of lysine. Both the ailing pig industry and the price drop for lysine in 1998/1999 resulted in lower sales and earnings from the feed additive sector in 1999. The markets in the US and Asia are the largest sales outlets for ADM. Europe is comparatively small. Latin America is also a small market but is increasing in importance.

3.8.1 Feed additive business

The product portfolio of ADM's feed additives is as follows:

- amino acids – basic manufacturer of lysine, threonine, and a tryptophan-lysine blend
- vitamins
- organic acids – basic manufacturer of citric acid and lactic acid

ADM, being a highly efficient agricultural complex, is investing in R&D activities for several fermentation products. The bioproducts division has shown long-term interest in expanding and developing the vitamin line. Vitamin projects in the past covered vitamin C, biotin, vitamin B_{12}, and niacin. On the carotenoid side, ADM had entered into an agreement with the small Maryland based firm Igene Biotechnolgy for astaxanthin. However, this resulted in a

legal case in which both companies were suing for patent infringement and stealing trade secrets.

Sales of amino acids were estimated to be in the region of $200 million for 1999. This figure is well below previous years. The highly competitive market and the weakening Euro currency are responsible for this drop in sales revenues.

In the past few years, ADM was repeatedly accused of involvement in price fixing of its key bioproducts. The company was fined both by the US authorities and the EU. This continues to blemish the image of the image of the company.

3.8.2 Corporate and product activities

- ADM announced launch of vitamin C production from its Decatur, US plant in 1999
- Break up of co-operation with Igene Biotechnology on astaxanthin project in 1997
- Joint venture agreement with Rhône-Poulenc in 1996 to create a global animal feed premix operation. This is followed by existing collaborations on the joint production of methionine and vitamin B2
- Take-over of Vitamin B_2 manufacturer Zeagen; move of the production to Decatur, US in 1994
- Acquisition of central Soya's feed and premix operations in 1994

3.8.3 Prospects for future merger and acquisitions candidates

ADM is known as an aggressive and low-cost producer in the market. With its strong position and experience in the fields of fermentation, oils and starches, it will expand its business in the food, nutraceutical and feed business. ADM scans the markets for possible acquisition of companies that manufacture products for the food, feed and pharmaceutical industry. Products of interest include vitamins, carnitine and carotenoids, since all these products can in principle be produced by fermentation.

3.9 Alpharma Incorporated

Animal Health Division
One Executive Drive
Fort Lee
NJ 07024
USA

Tel: +1 201 947 7774
Fax: +1 201 585 0429
Website: www.alpharma.com
E-mail: Robert.Jones@alpharma.com
Robert Jones, Sales and Marketing, Senior Vice President

The foundation of the company was laid in 1903 when Apothekernes Laboratorium, Oslo was established in Norway. The subsidiary company, the US-based AL Laboratories, was created

in 1975 and grew to one of the largest antibiotic producers in the world. This was basically achieved by acquisitions. Alpharma Incorporated was then created in 1994 when AL Laboratories merged with the parent company Apothekernes Laboratorium, resulting in several strategic acquisitions.

Today, Alpharma is a global company with 3,500 employees and an annual turnover of $742 million for the whole group. Active in 60 countries, the company has 38 sites in 22 countries. Alpharma manufactures and markets speciality generic and proprietary human pharmaceutical and animal health products. The animal related divisions cover land-based animal health and aquatic animal health.

The animal health business accounted for $182 million in 1999, 91% of which was generated with medicinal feed additives for poultry, pig and cattle. Fish vaccines accounted for the remaining 9%.

The announcement by Alpharma in early 2000 that it was to acquire the entire MFA business of Roche will strengthen its global position in the field of antibiotics and coccidiostats. The sales revenue of Alpharma and Roche in 1999 resulted in turnover close to $400 million, making Alpharma the number one MFA company in the world.

To date, Alpharma's MFA business is focused on the US, where most sales are generated. Following the acquisition of Roche's MFAs, Alpharma has recently opened a number of new offices and signed distributor agreements in several markets to improve its market presence.

3.9.1 Feed additive business

The principal products are:

- Performance enhancers – chlortetracycline, bacitracins
- Anticoccidials – decoquinate, 3-nitro
- Antihistomonals – nitarsone, 3-nitro
- Liquid animal nutrition and health products

The takeover of Roche's MFA business has introduced additional products into the portfolio.

In the US, Alpharma products are well established in the market. R&D is mainly restricted to post-launch activities for the feed additive niche market of MFAs. With the consolidation of the MFA industry higher profit margins are anticipated in future.

Most of the sales revenue has traditionally been achieved from the product BMD (bacitracin methylene disalicylate). Alpharma has been very active in gaining approval for additional product claims and product combinations. In the US alone there are 29 different two-way and three-way MFA combinations with BMDwhich have been approved. It is estimated that of for every $166 of MFA sales in 1999, close to $100 were made with BMD.

3.9.2 Corporate and product activities

- Acquired the MFA business of Roche for $300 million in 2000

- Acquired production and marketing rights for a porcine somatotropin

- Acquired ID Russel, a specialist in manufacturing and marketing of soluble antibiotics in 1999

- Acquired anticoccidial Deccox from Rhône-Poulenc in 1997

3.9.3 Prospects for future mergers and acquisitions

Alpharma's strategy is focused on the medicinal feed additive market. Based on bacitracins, the company acquires branded products that complement the anti-infective feed additive line. Advanced knowledge of fermentation technologies mean it favours products derived from microorganisms. Candidates for further acquisitions are antibiotic manufacturers, like Antibioticos or Biochemie.

3.10 Ajinomoto Company

15-1, Kyobashi 1-chome
Chuo-ku
Tokyo 104-8315
Japan

Tel: + 81 3 5250 8111
Fax: + 81 3 5250 8293
Website: www.ajinomoto.com
Mr. Hiroshi Sakaguchi, General Manager, Amino Acid Department, Amino Acid Division

The origin of Ajinomoto goes back to 1988 when Naka Suzuki, the mother of company founder Saburosuke Suzuki II, started production of iodine from seaweed in Hayama at the Kanagawa Prefecture. Ajinomoto – which is another name for monosodium glutamate (MSG), was established in 1909. Fermentation-based production was developed after 1950 which was also the basis for the development of other amino acids and nucleic acids. Today, Ajinomoto focuses on food products, with MSG as the main product as well as its fine chemicals and other businesses.

Group turnover reached $7,825 million in the year ending Mach 2000. The major share of 81% is generated within Japan. Sales in the fine chemical division were valued $1,268 million and the food division achieved $5,650 million during the same period.

The fine chemical division markets and sells its products to the feed, food, cosmetic and pharmaceutical sectors. Products include sweeteners, functional foods, surfactants, drugs and amino acids. Only amino acids are offered to the feed industry.

3.10.1 Feed additive business

The product portfolio is limited to amino acids – basic manufacturer of lysine, threonine and tryptophan.

Ajinomoto's activities are supported by its Central Research Laboratories including four business-specific R&D centres.

Ajinomoto is one of the few suppliers that offer three different amino acids. The market share of Ajinomoto's lysine was around 26% in 1999. Annual production capacity was increased in 2000 from approximately 150,000 tonnes to about 200,000 tonnes. Further expansion to

300,000 tonnes is planned up to 2005. Lysine plants are located in France, Italy, the US, Brazil, Thailand and China. The French threonine plant had raised its production capacity in 1999 to 15,000 tonne per annum. Tryptophan, until now produced at the Kyushu plant in Japan, is transferred to a new plant in France in 2000. Annual capacity is to increase to reach 1,000 tonnes until 2001.

The major global markets, the US, Europe, Latin America and Asia, are well represented by Ajinomoto's subsidiaries and manufacturing plants. Amino acids sales are shared equally between the Americas, Europe and Asia. The sales revenues for feed-use amino acids were estimated at $174 million in 1999. The drop of the lysine price on the world market badly affected Ajinomoto's sales revenues in 1999. Operating income also fell sharply compared with the previous year.

3.10.2 Corporate and product activities

- Eurolysine in France renamed Ajinomoto Eurolysine
- Ajinomoto Biolatina in Brazil completed an expansion of production capacity from 35,000–40,000 tonnes in 2000
- Transfer of tryptophan production from Kyushu,Japan plant to Europe in 2000. Capacity to be raised each year to reach 1,000 tonnes in 2001
- Ajinomoto increased its share in Eurolysine from 75% to 100% in 1997
- Joint venture company Chuanhua Ajinomoto established in China in 1994, for the production of lysine

3.10.3 Prospects for future mergers and acquisitions

Ajinomoto products are well established in the global market. Any additional commodity feed additive would complement the company's activity. Novus with its methionine hydroxy analogue would fit well into the product portfolio.

3.11 Hoechst Roussel Vet GmbH /Akzo Nobel /Intervet

Rheingaugasse 190
D-65203 Wiesbaden
Germany

Tel: + 49 0611 962 05
Fax: + 49 0611 962 9 832
Website: www.HoechstRousselVet.com
E-mail: ireuther@HRVet.com
Gerd Widmann, Managing Director
Willem Kleijn, Board of Directors and Head of Marketing and Sales

Hoechst originates back to 1863. It was founded in the village of Hoechst, which is located in the vicinity of Frankfurt, Main. The major industrial activities comprised of pharmaceuticals, chemicals, agrochemicals and animal nutrition and health. In December 1999, Hoechst merged with the French multi-national company Rhône-Poulenc to form the new company

Aventis. Its new business strategy led to the divestment of the animal nutrition and health division of Hoechst, ie Hoechst Roussel Vet GmbH. In November 1999, Akzo Nobel agreed to buy the whole veterinary and feed additive business of Hoechst Roussel Vet GmbH for DM 655 million. Subsequently, Akzo Nobel is integrating Hoechst Roussel Vet GmbH into its subsidiary company Intervet.

The sales of the Hoechst Roussel Vet GmbH reached about DM 750 million in 1999 (DM 878 million in 1998). The feed additive portfolio was equivalent to approximately DEM 250 million in 1999 (DEM 230 million in 1998).

The scope of products comprises of veterinary pharmaceuticals, biologicals and MFAs. The product line of Hoechst Roussel MFAs accounts for approximately 30% of the company turnover. After the acquisition through Akzo Nobel, Hoechst Roussel's veterinary products were given priority over MFAs. This has led to a significant loss of MFA professionals to other companies.

3.11.1 Feed additive business

The product portfolio covers:

- MFAs – performance enhancers and anticoccidials
- Probiotics
- Enzymes, NSP type – manufactured by Japanese company
- Taste and flavour substances

Within Europe the performance enhancers sell exceptionally well since the ban of most other feed antibiotics. The Hostazym enzyme range grossed DM 10 million in 1999. The product is similar to Roche's Roxazyme G. The marketing of the appetising substance Sangrovit has been practically non-existent since 1999 and the product was discontinued in 2000.

3.11.2 Corporate and product activities

- Akzo Nobel acquired Hoechst Roussel Vet GmbH at the end of 1999

- Acquisition of Prodeta, a subsidiary of Guyomarc'h Nutrition Animale in 1998. With Prodeta Hoechst Roussel gained global control of production and distribution

- The performance enhancers flavomycin and salinomycin were exempt from the ban imposed by the EU in 1998

3.11.3 Prospects for future mergers and acquisitions

The feed additive line may be sold in future. Potential candidates are Alpharma and Koffolk.

3.12 Takeda Chemical Industries Limited

1-1, Doshomachi 4-chome
Chuo-ku
Osaka 541
Japan

Tel: + 81 6 204 2111
Fax: + 81 6 204 2000
Website: takeda.co.jp
E-mail: Hiroshi Uchiyama: President of Vitamin & Food Company

Takeda's origin goes back already to 1781 when Chobei Takeda started as a small medicine wholesaler. Today, the company is a research based global company with a main focus on pharmaceutical products. It is the largest pharmaceutical company in Japan. Takeda's sales revenues reached $6,980 million in 1999. More than 70% of sales are generated from pharmaceuticals, 13% by chemicals and 9% by vitamins and food ingredients. The animal health business is focused on therapeutic antibiotics and performance enhancing antibiotics. This business accounts for 2.5% of the group sales.

Takeda's animal health business is concentrated in the Japanese market. On the vitamin side, Takeda made strong efforts over the past years to establish a stong global position. The unfavourably strong exchange rate of the Japanese Yen, however, reduced the competitiveness of Takeda in the global market. Product formulations and quality are well received around the globe.

3.12.1 Feed additive business

Product portfolio is composed of:

- Vitamin – basic manufacturer of B_1, B_2, B_6, C and folic acid
- Antibiotics – tylosin analogue, sedecamycin, enramycin, chlortetracycline

The sales of all vitamins and medicinal feed additives supplied to the feed industry segment were estimated at about $70 million for 1999. Vitamin sales alone accounted for approximately $35 million. Although Takeda's sales of vitamins total $250 million, only a fraction is sold to the feed industry. The largest sales are generated from vitamin C. This vitamin, however, is mostly sold for human consumption and not for animal nutrition.

The reduction of prices for vitamin C and vitamins of the B group since 1996 has drastically affected the profitability of Takeda's vitamin business. The bulk vitamins and food division has reported an operating loss for the last three years. Takeda is one of the companies involved in the illegal vitamin price fixing cartel, for which they were sued by the US authorities and fined $187 million.

Takeda markets its vitamin products through its three regional offices in the US, Singapore and Germany. All three subsidiaries were transferred to BASF as part of a joint venture agreed in July 2000.

The geographical break-down of sales is as follows:

Americas – 9%
Europe - 5%
Asia – 86%

3.12.2 Corporate and product activities

- Takeda and BASF form a 34:66 joint venture for the sale and distribution of the joint range of bulk vitamins. Under the agreement Takeda will supply the entire output of bulk vitamins from it Hikari, Yamaguchi plant to BASF
- Formation of a 60:40 joint venture between Schering-Plough KK and Takeda Chemical Industries to form Takeda Schering-Plough Animal Health KK was announced in March 2000. Takeda is to transfer its animal health business from the agro division
- Announcement in 1999 to spin-off or sell low-profit operations and to cut back more than 40% of all employees by the year 2005
- Takeda raised capacity of vitamin C plant in Hikari, Japan by 3,000 tonnes to 15,000 tonnes per annum in 1999

3.12.3 Prospects for future merger and acquisitions

Takeda is focusing on its profitable core businesses. The joint venture agreements with BASF and Schering-Plough for the animal nutrition and animal health business are part of this consolidation strategy.

3.13 Koffolk Incorporated

PO Box 675935
Rancho Santa Fe
CA 92067
USA

Tel: + 1 619 759 8012
Fax: +1 619 759 8012
Website: www.koffolk.com
E-mail: koffolk@worldnet.att.com

Founded in 1949, Koffolk is part of the Philipp Brothers Chemicals group of companies. The Philipp Brothers group manufacturers more than 400 chemicals through its parent company and subsidiaries. Products include feed additives, inorganic chemicals and intermediates for the pharmaceutical industry. Further, it is involved in several metallic-recycling activities.

The turnover of the Philipp Brothers group was $472 million in 1999 and the number of employees exceeded 1,600.

3.13.1 Feed additive business

The feed additive product range of Koffolk includes

- anticoccidials – nicarbazin and amprol
- vitamin A – formulation process

Koffolk has a dominant position on the global market for the anticoccidial nicarbazin. For many years Koffolk purchased retinyl-ester from the three main manufacturers Roche, BASF and Rhône-Poulenc. The raw material was converted into a feed grade material and then sold as a Koffolk product. Today, all three companies have ceased the sale of the raw material. Koffolk also sourced vitamin A oil from Russia the resulting product was of poor quality and is mainly sold to developing countries.

3.13.2 Corporate and product activities

Koffolk bought Pfizer's veterinary and feed additive line in 2000. Whether the acquisition covers only the MFA group or also some of the veterinary products has not yet been revealed.

3.13.3 Prospects for future merger and acquisitions candidates

Koffolk will become one of the main players in the MFA business and perhaps also on the veterinary side. The deal with Pfizer must first be fully disclosed before any further comment can be made.

APPENDIX

For the inter-conversion of currencies, standard exchange rates were applied as per the table below:

Currency Exchange Rates

Year	€	$	DM	G	SwFr	£
2000	1	0.8900*	1.9558	2.20371	1.5100*	0.6092
1999	1	1.0658	1.9558	2.20371	1.6003	0.6588
1998		1	1.7592	1.9830	1.4489	0.6037
1997		1	1.7348	1.9524	1.4516	0.6106
1996		1	1.5037	1.6850	1.2336	0.6405
1995		1	1.4228	1.5938	1.1735	0.6290
1994		1	1.6218	1.8188	1.3662	0.6535
1993		1	1.6544	1.8585	1.4778	0.6828
1992		1	1.5595	1.7559	1.4025	0.5872
1991		1	1.6612	1.8719	1.4353	0.6219
1990		1	1.6161	1.8209	1.3872	0.6046

*Note: * September 2000*

OTHER REPORTS FROM ANIMAL PHARM

Title/Sector	Reference No
Markets & Companies	
Companion Animals: New markets for human pharmaceuticals and agrochemicals	SR 196
The Indian Animal Health Market	SR 192
The Top 20 Companies Report (1999 Edition)	SR 189
Generic Animal Health Companies	SR 174
Animal Health in 2005	SR 172
World Animal Health Markets	SR 169
Animal Health Markets in South America	SR 163
Animal Health Markets in the Far East	SR 161
The Japanese Animal Health Market	SR 154
Products	
Reproduction Products for the Animal Health Industry	SR 195
Generic Animal Health Products	SR 190
Salmonella: Products and markets	SR 187
Vaccines: Products and markets	SR 188
Antiparasitics	SR 186
Antibiotics: Resistance Issues	SR 185
Livestock Respiratory Disease: Products & markets	SR 180
Complete Guide to Aquaculture	SR 176
Species Markets I: Pig Veterinary Products	SR 165
Species Markets II: Poultry Veterinary Products	SR 166
Species Markets III: Small Animal Veterinary Products	SR 171
Species Markets IV: Cattle Veterinary Products	SR 178
Bovine Mastitis: Products and markets	SR 173
Novel Animal Health Products	SR 162
Veterinary Immunodiagnostics: A Worldwide perspective	SR 159
Veterinary Vaccines: A World Market Review	SR 156
Therapeutic Antibacterials	SR 149
Strategic Management/Regulatory Guides	
A Guide to Outsourcing in the Animal Health Industry	SR 193
Animal Health Marketing Strategies on the Internet	SR 181
Advances in Veterinary Drug Delivery	SR 175
Environmental Risk Assessment	SR 170
Animal Health Marketing Strategies in the EU	SR 158
Environmental & Political Issues in the Animal Health Industry	SR 157
Research & Development	
Animal Health R&D Trends	SR 183
Animal Health in 2005	SR 172
Transgenic Animals	SR 141

Poultry on Antibiotics:

Hazards to Human Health

Authors

David Wallinga, M.D., MPA
Navis Bermudez, MESc
Edward Hopkins

Institute for Agriculture and Trade Policy
Sierra Club
December 2002

2nd Edition

Sierra Club and IATP wish to thank Kendra Kimbirauskas, Jessica Nelson and Erin Jordahl for their assistance with this project. IATP would like to thank the Quixote Foundation for their support of this work. This report has been funded by a grant from The Sierra Club Foundation.

Founded in 1986, IATP works with family farm organizations around the country and the world, supporting policies and practices that result in healthy, profitable farms, greater public benefit, a safer food supply and flourishing rural communities.

The Sierra Club members are 700,000 of your friends and neighbors. Inspired by nature, we work together to protect our communities and the planet. The Club is America's oldest, largest and most influential grassroots environmental organization

Institute for Agriculture and Trade Policy
2105 First Avenue South, Minneapolis, MN 55404 (612) 870-0453
www.iatp.org

Sierra Club
85 Second St., Second Floor, San Francisco, CA 94105, (415) 977-5500
408 C St. NE, Washington, DC 20002, (202) 547-1141
www.sierraclub.org

Download a copy of the report from *www.iatp.org* or *www.sierraclub.org/antibtiotics*

Cover Photo: Photo Illustration © Union of Concerned Scientists/Nancy Friedland.

Executive Summary

Consumers expect the meat they purchase to be free of health-threatening bacteria. Increasingly, though, we've learned that food products, particularly meats, may be contaminated with bacteria that pose serious health risks.

In October 2002, the U.S. experienced the largest recall of meat in its history. It was associated with 13 deaths and 120 illnesses. Overall, the Centers for Disease Control and Prevention (CDC) estimates that bacteria cause nearly 5.2 million foodborne infections each year, resulting in 36,000 hospitalizations and almost 1300 deaths.

Most foodborne illness caused by bacteria gives victims a few days of intense discomfort and requires no treatment with antibiotics. But for patients whose infections spread beyond the intestine, antibiotics can be lifesaving.

For decades, antibiotics have dramatically reduced illness and death from bacterial infections. But recently, the effectiveness of these life-saving drugs has begun to wane because antibiotics are being overused.

Certainly antibiotics are overused in human medicine. Yet another major, and often overlooked, source of overuse is that factory farms routinely feed antibiotics to livestock to promote growth and to compensate for crowded, unsanitary conditions conducive to infection.

Scientific consensus now says that this antibiotic use in food animals contributes to antibiotic-resistant bacteria transferred to humans, mainly through contaminated food. The Union of Concerned Scientists estimates that 70 percent of *all* antibiotics in the U.S. are fed to pigs, poultry and cattle for reasons other than treating disease. The majority of such medicines are "medically important" – that is, identical, or nearly so to antibiotics used for humans.

Medical professionals are speaking out against this unnecessary use of antibiotics in food animals. If they can't rely upon effective antibiotics, it will become more difficult, and in some cases impossible, to treat bacterial illnesses. The American Medical Association (AMA) has gone on record opposing the use of antibiotics in farm animals that aren't sick.

Given the current interest in foodborne illness and antibiotic resistance, this study focuses on determining the prevalence of antibiotic-resistant bacteria on poultry products routinely purchased at grocery stores. Consumers should know what bacteria may contaminate their food and the potential dangers of eating certain food products.

This is the first study to examine brand-name poultry products at the retail level for the presence of antibiotic-resistant bacteria, including resistance to medicines relied upon to treat human infections. We chose brand-name poultry products that were prominent in the grocery stores we visited. Ours is also the first study to test for drug resistance among multiple bacteria found on poultry products at the same time, arguably a better measure of risk to the people actually eating the poultry.

We bought 200 fresh whole chickens and 200 packages of ground turkey from grocery stores in Des Moines, Iowa and Minneapolis-St. Paul, Minnesota. We contracted with a certified food-testing laboratory to test the products for the presence of three bacterial strains – *Salmonella, Enterococci* and *Campylobacter* – and for resistance to a number of antibiotics.

Campylobacter and *Salmonella* are the top two bacterial causes of foodborne illness in the U.S. Together, they account for an estimated 3.3 million foodborne infections and more than 650 deaths each year. Not everyone is at the same level of risk. Infants are ten times more likely than the general population to contract *Salmonella* infections, and twice as likely as older people to suffer a *Campylobacter* infection.

Contaminated meat is the dominant source of human *Salmonella* infections, while 50 percent or more of *Campylobacter* infections may come from eating contaminated chicken, according to Food and Drug Administration (FDA) estimates.

Disease-causing bacteria, *Salmonella* or *Campylobacter*, contaminated a large proportion of the whole chickens and ground turkey we purchased. The widespread resistance of bacteria in poultry samples to one or multiple antibiotics is perhaps an even greater cause for concern.

- Ninety-five percent of the 100 whole chickens we tested were positive for *Campylobacter*, the top cause of bacterial foodborne illness, or food poisoning, in the U.S. Nearly 62 percent of the *Campylobacter* bacteria tested for resistance were resistant to 1 or more antibiotics.

- More than 8 percent of *Campylobacter* tested for resistance were resistant to Cipro, the antibiotic of choice for presumptively treating severe bacterial food poisoning. The FDA's best estimate recently was that more than 153,000 people in 1999 alone contracted Cipro-resistant *Campylobacter*, just from eating contaminated chicken.

- Nearly 18 percent of whole chickens purchased were contaminated with *Salmonella*. Twenty percent of Country Pride chickens carried *Salmonella*, as did 15 percent of Gold'N Plump chickens. All 35 *Salmonella* isolated from whole chickens were analyzed for antibiotic resistance, and 6 percent were resistant to 4 or more antibiotics.

- Ground turkey purchased was more contaminated with *Salmonella* than was whole chicken, with an overall rate of 45 percent. Fifty-six percent of the Honeysuckle White ground turkey and 34 percent of the Jennie-O ground turkey carried *Salmonella*. Sixty-two percent of the *Salmonella* bacteria tested that were found in turkey were resistant to 1 or more antibiotics; a third of these *Salmonella* were resistant to 4 or more antibiotics.

- Both *Salmonella* and *Campylobacter* contaminated 32 percent of the Country Pride chickens and 14 percent of the Gold'N Plump chickens that we tested for both organisms (100 total), as well as 2 percent of the Jennie-O turkey we tested (1 of 51 packages)

- More than 90 percent of the *Enterococci* from chicken or turkey that was tested (101 total) for resistance was resistant to Synercid. Strains of resistant *Enterococci* are a growing cause of infections and deaths in hospitals, and Synercid is one of a few antibiotics still effective against them.

There are no good estimates of how many people overall suffer from foodborne infections resistant to antibiotics. As noted, more than 150,000 people may have developed fluoroquinolone-resistant *Campylobacter* infections just from eating contaminated chicken. Most antibiotic-resistant *Salmonella* in humans stems from eating contaminated food as well.

More people eating food contaminated with antibiotic-resistant *Salmonella* or *Campylobacter* will become ill than will people eating food with non-resistant organisms. One estimate is that the mere presence of *Salmonella* and *Campylobacter* strains resistant to at least one antibiotic could result in nearly 47,000 additional people getting foodborne illnesses, when compared to the expected number of sick following exposure to non-resistant strains.

In addition, people with antibiotic-resistant *Salmonella* and *Campylobacter* are likely to be sicker, for longer, than are people with non-resistant infections.

Recommendations

Consuming meat with antibiotic-resistant bacteria is not inevitable. Consumers, poultry producers and restaurants can all take steps to reduce or eliminate these health threats.

<u>Poultry producers should reduce overall antibiotic use to a minimum. In addition, they should stop feeding antibiotics to birds or flocks that are not sick.</u> Poultry producers also should stop using any antibiotic "cousins" of Cipro, which is simply too important to humans to risk its effectiveness by continuing the imprudent use of closely related drugs in poultry.

The good news is that some poultry producers are working hard to provide safer chickens and turkeys, by using better hygiene, by implementing growing or slaughter conditions to lower the levels of disease-causing bacteria on their meats, or by avoiding the use of antibiotics which increase the risk that meat will be contaminated with antibiotic-resistant bacteria.

Four of the top five top chicken producers already have sworn off any use of Cipro-like antibiotics, including ConAgra Poultry, producers of Country Pride chicken. Others, also including ConAgra, have made various claims to having stopped or greatly reduced the use of antibiotics for growth promotion or disease prophylaxis. We generally laud this approach, although there is no existing mechanism for verifying producers' claims.

Large-volume buyers should only purchase poultry from producers that use no antibiotics for animals that are not sick, such as for growth promotion, and that use no critically important human antibiotics, like Cipro, for any reason. McDonald's, Popeye's and Wendy's all now claim they refuse to buy chicken treated with Cipro-like antibiotics. Several other fast food companies, like Hardee's, Subway and Domino's, have similar policies, but also say they won't buy chickens fed important human antibiotics for non-therapeutic reasons, like growth promotion.

For consumers to be certain of buying poultry raised without antibiotics, they can buy certified organic chickens and turkeys.

Some poultry producers use U.S. Department of Agriculture (USDA)-defined terms like "raised without antibiotics" or "no antibiotics administered" on their meat labels. Consumers can derive some assurance from these claims, although no third party certifies them, as is the case with organic products.

Check out the **Eat Well Guide**, *www.iatp.org/EatWell*, for a state-by-state listing of meat and poultry producers using no antibiotics, or no routine antibiotics, in addition to restaurants and other places to buy these products. If they are not available, consumers should ask grocery store or restaurant managers to provide this option.

Consumers also should always cook meat thoroughly and carefully follow safe meat-handling procedures. Consumers can find practical advice and general information on food safety at *www.foodsafety.gov*.

Chapter 1

Introduction

Bacterial foodborne illness is a serious health problem in the United States. In October 2002, the U.S. experienced the largest recall of meat in its history.[1] It was associated with 13 deaths and 120 illnesses. Each year, foodborne bacteria result in nearly 5.2 million illnesses, 36,000 hospitalizations and almost 1300 deaths, according to Centers for Disease Control and Prevention (CDC) estimates.[2]

Campylobacter and *Salmonella* are the leading causes of foodborne bacterial infections. Together, they are responsible for an estimated 3.3 million foodborne infections and more than 650 deaths each year.[3] In rare cases, people infected with *Campylobacter* can later develop Guillain-Barré Syndrome, an acute paralytic condition that can sometimes be fatal.[4]

An estimated 80 percent of *Campylobacter* infections and 95 percent of *Salmonella* infections are contracted via contaminated food.[5] Contaminated meat is considered the dominant source of *Salmonella* infections.[6] Poultry is a major source of human *Campylobacter* infection, 48.5 to 66.7 percent may come from eating chicken, according to recent estimates by the U.S. Food and Drug Administration (FDA).[7,8]

U.S. poultry is significantly contaminated with *Campylobacter* and *Salmonella*. In 1994-95, the U.S. Department of Agriculture (USDA) surveyed whole chickens from slaughter facilities representative of the nation as a whole and found 88 percent were contaminated with *Campylobacter* bacteria, while 20 percent carried *Salmonella*.[9]

Antibiotics vs. Antimicrobials

Antibiotics are naturally occurring chemicals that kill or inhibit bacteria. But the term is often used more loosely to also include synthetic antibacterial agents, as well as compounds that affect other microorganisms, like parasites (technically "antimicrobials").

Salmonella and *Campylobacter* on meat have long been a problem. The escalating resistance of these and other foodborne bacteria to one or multiple antibiotics has raised more recent concerns.

Most foodborne illness caused by bacteria gives victims a few days of intense discomfort – diarrhea, fever, abdominal cramps, and requires no treatment with antibiotics. For patients whose infections become invasive, entering the bloodstream, brain or other organs outside the intestine, antibiotics may be life-saving. Around 40 percent of people with *Salmonella* infections who seek treatment receive antibiotics, according to surveys by the CDC.[10] Rising antibiotic resistance among foodborne pathogens therefore carries health consequences for humans, as well as for animals.[11,12,13]

Eating food that contains antibiotic-resistant pathogens can have a *direct* impact on health. Resistant strains of bacteria can cause more severe or more prolonged illnesses than will non-resistant bacteria.[14] Indirect health impacts are less obvious. Mounting evidence suggests that antibiotic-resistant bacteria on food, once ingested, may be able

to pass their resistance onto other bacteria in the human intestine. If pathogenic, these newly resistant bacteria could go on to cause disease in the person eating the food, although perhaps long after the food was actually consumed.

Use of Antibiotics in Poultry and Other Food Animals

Ultimately, it is the use of antibiotics that drives bacteria to become resistant. Certainly, human uses are important. But the scientific consensus emerging is that antibiotic use in food animals also contributes to antibiotic-resistant bacteria transmitted to humans, typically through contaminated food.[15,16,17,18,19,20,21]

Bacteria found in the intestines of animals can be animal pathogens, human pathogens like *Salmonella* and *Campylobacter*, or "commensal" bacteria, which are part of the normal bacterial flora. Resistance can emerge and spread when these bacteria are exposed to non-lethal levels of antibiotics, such as those in animal feed or water for growth promotion. During slaughter or processing, these resistant bacteria can contaminate food.

Resistant bacteria, as well as the genetic material that makes them resistant, also can spread to human handlers, to other animals or to the broader environment – such as through manure, which can itself contaminate the surface waters, groundwater, and air that is next to, under or above livestock farms.

No government mechanism in the U.S. tracks antibiotic use, in humans or in food animals. Estimates by industry and advocacy groups agree that antibiotic use in food animals is huge, as much as 29.5 million pounds, dwarfing total human use by 4 to 10-fold.[22,23]

Antibiotic use is widespread in confined animal feeding operations (CAFOs) – more commonly, "factory farms" – that have come to dominate food animal production in the U.S.[24,25] Poultry factories now dominate U.S. production, accounting for more than 97% of U.S. sales of broiler chickens.[26] The EPA defines factory broiler chicken and turkey facilities as those containing at least 100,000 broilers or 55,000 turkeys.

Surveys of poultry plants in 2000 found that two-thirds were giving broiler chickens "grower" feeds containing antibiotics, while almost 65 percent were using antibiotic "starter" feeds – this, according to an industry database representing more than 90 percent of the broiler industry.[27] Arsenic compounds also were used in starter and grower feeds by almost 70 percent and 74 percent of broiler "plants" surveyed, respectively.[28]

Antibiotics generally are put into feed not as therapy for treating sick birds or flocks, but rather to promote growth or to prevent infections among flocks raised in cramped, stress-inducing, often unhygienic conditions conducive to infection. The Union of Concerned Scientists, using available data, recently estimated that 10.5 million pounds of antibiotics annually are put in poultry feed or water for these non-therapeutic reasons.[29]

Twenty-one percent (2.2 million pounds) are antibiotics identical or nearly so to ones used in human medicine. They include tetracyclines, erythromycin, penicillin, bacitracin, and virginiamycin (a close relative of the critical human medicine, Synercid). By comparison, all human antibiotic use may consist of just 3 million pounds each year.[30]

The balance of non-therapeutic poultry antibiotics – 8.3 million pounds – are arsenical compounds (like roxarsone) or other agents not considered important for human use.

By industry estimates (1999), around 38,000 pounds of fluoroquinolone antibiotics annually also are given in drinking water to poultry flocks when some birds become sick with respiratory disease.[31] Fluoroquinolones, such as ciprofloxacin (Cipro) are considered critical human medicines. When fluoroquinolone agents were first approved for use in poultry in 1995, therefore, it provoked much public health concern. When a 1999 Minnesota study found 20 percent of *Campylobacter* isolated from retail chickens to be Cipro-resistant, that concern only grew.

Purpose of this Report

No government testing to date, nor studies appearing in scientific journals, have tested specific poultry brands for both the presence of disease-causing bacteria *and* their resistance to antibiotics. No studies that we have identified have tested *multiple* bacteria found on poultry at the same time for their resistance to antibiotics, perhaps the best reflection of bacterial risk to people actually eating the meat.

In 1998, the magazine *Consumer Reports* did test 1,000 whole chickens purchased from grocery stores in 36 cities for levels of *Salmonella*, *Campylobacter* and generic *Escherichia coli* (an indicator of fecal contamination). The study included tests of four leading brands – Perdue, Tyson Holly Farms, Foster Farms and Country Pride, as well as several "premium" supermarket and kosher brands (of these, Country Pride is the only brand we also tested). The *Consumer Reports* study did not test turkey meat, and did not test for antibiotic resistance among any of the bacteria found on meat.

That study also preceded the U.S. Department of Agriculture's 1998 launch of its new HACCP (Hazard Analysis and Critical Control Point) slaughterhouse inspection program, specifically designed to reduce the levels of certain pathogens on meat and poultry. For poultry consumers, especially those in Minnesota and Iowa, therefore, our study gives new or updated information about the effectiveness of the program in ensuring lower pathogen levels on the specific poultry brands they buy.

The Sierra Club and the Institute for Agriculture & Trade Policy jointly commissioned this study, using funds from non-profit foundations or individual donors. We neither solicited nor used any money from corporations for this project.

CHAPTER 2

BACKGROUND INFORMATION ON BACTERIAL CONTAMINATION OF MEAT AND PUBLIC HEALTH CONCERNS

Government studies, as well as articles published in scientific journals, have long demonstrated that U.S. meats, including chicken and turkey, are significantly contaminated with disease-causing bacteria, including *Salmonella* and *Campylobacter*. More recent studies also demonstrate that *Salmonella*, *Campylobacter*, and other bacteria on meat individually often are resistant to antibiotics.

Government Testing for Bacteria in Meat

In 1994-95, the U.S. Department of Agriculture's Food Safety Inspection Service (FSIS) sampled nearly 1300 broiler chickens from slaughter facilities responsible for 99 percent of all slaughtered U.S. chickens. It found 88 percent were contaminated with *Campylobacter* bacteria, while 20 percent carried *Salmonella* bacteria.[32] Similarly, FSIS collected nearly 300 ground turkey samples in 1995 from 40 slaughterhouses, and found half (49.9 percent) carried *Salmonella*, and one in four samples (25.4 percent) was contaminated with *Campylobacter* species.[33]

For both broilers and ground turkey, the 1994-95 *Salmonella* data became the microbiological "baseline" or standard for the USDA's new HACCP system for slaughterhouse inspection, which began in 1998. Under HACCP, USDA collects hundreds or thousands of meat samples each year from large and small slaughterhouses and tests them for *Salmonella*.[34] To be in compliance, for example, no more than 20 percent of the 51 broilers tested in a plant (or 49.9 percent of the ground turkey) can carry *Salmonella*. Plants out of compliance must start corrective actions in order to meet the standard in follow-up testing. Strictly speaking, HACCP is simply an inspection program to monitor the cleanliness of slaughter facilities, and not a program for assuring consumers access to safe meat at the retail level.

In the years since HACCP began, USDA data (Table 1) show that in large plants meeting the *Salmonella* standards for either broilers or ground turkey, the prevalence of *Salmonella* has tended to fall. For 2001, the most recent data show *Salmonella* contamination of just 9.7 percent and 25.2 percent on broilers and ground turkey, respectively, for these same large plants – roughly half the levels found in USDA's "baseline" surveys in 1994-95.

Table 1: Prevalence of *Salmonella* and *Campylobacter* (in % of samples) on Raw Broiler Chickens and Ground Turkey Meat in Large U.S. Slaughterhouses Meeting USDA's Standards Under HACCP, 1998-2001, and Compared to Baseline.				
Year of Testing	**Salmonella**		**Campylobacter** (NT = not tested)	
	Whole Chicken	Ground Turkey	Whole Chicken	Ground Turkey
Baseline	20.0	49.9	88.2	25.4
1998	10.8	36.5	NT	NT
1999	9.3	33.1	NT	NT
2000	7.5	26.5	NT	NT
2001	9.7	25.2	NT	NT
Source: Food Safety Inspection Service, U.S. Department of Agriculture, Progress Report on Salmonella Testing of Raw Meat and Poultry Products, 1998-2001, Accessed 11/23/02 at *www.fsis.usda.gov/OPS/haccp/salm4year.htm.*				

By way of comparison, USDA (2001) recently tested whole turkeys in 38 slaughter plants throughout the U.S. for *Salmonella* contamination. The Center for Science in the Public Interest released the data to the public, including contamination levels for specific named plants, which ranged from 0 percent to more than 30 percent.[35] For example, Honeysuckle White brand whole turkeys tested in various Cargill plants were found to have *Salmonella* contamination ranging from 1.8 percent of tested birds (in California, MO) to 8.9% of birds (in Ozark, AR). Jennie-O brand whole turkeys tested in various Jennie-O plants were found to have *Salmonella* contamination ranging from 7.0 percent of tested birds (in Pelican Rapids, MN) to 14.3 percent of birds (in Faribault, MN plant).

Unlike for *Salmonella*, there is no performance standard for *Campylobacter* contamination under HACCP, nor does it require any testing of slaughter facilities for *Campylobacter* contamination of meat.

Other Select Studies of Bacteria in Meat

In Fall 1997, scientists at the Minnesota Department of Health purchased 91 "domestic chicken products" from retail supermarkets in the Minneapolis-St. Paul area, and found 88 percent contaminated with *Campylobacter* – the same prevalence as that found in USDA's 1994-95 baseline survey of broilers in slaughter facilities.

A study by White et al. (2001) purchased ground meats from supermarkets in the Washington, DC area and found 41 out of 200, or 20 percent, were contaminated with *Salmonella*.[36] Ground chicken (35%) and ground turkey (24%) were more frequently contaminated than were ground pork (16%) or ground beef (6%).

Recent surveys of U.S. retail meats also have found that an alarming percentage carry bacteria resistant to one or more important antibiotics. White et al. (2001), for example, analyzed 45 *Salmonella* from the 41 ground meat samples positive for *Salmonella* (some samples yielded multiple isolates). Eighty-four percent were resistant to at least one antibiotic, 53 percent were resistant to three or more antibiotics, and 27 percent were resistant to at least six antibiotics.[37]

In the Minnesota study just described, *Campylobacter* bacteria found on retail chicken products were also analyzed for antibiotic resistance. Twenty percent (18 of 91 products) of *Campylobacter* were resistant to ciprofloxacin. Eight of these Cipro-resistant isolates were also resistant to two other human fluoroquinolone medicines, grepafloxacin and trovafloxacin, as well as to two poultry fluoroquionolones, enrofloxacin (Baytril) and sarafloxacin. Six of the eight were also resistant to a fifth fluoroquinolone.[38]

As indicated by preliminary data from the Centers for Disease Control and Prevention, human *Campylobacter* infections resistant to fluoroquinolone (FQ) antibiotics rose from 13 percent in 1997 to 19 percent in 2001.[39] A decade ago, fluoroquinolone resistance was negligible. Human use of FQ antibiotics began in 1986. Yet FQ-resistant *Campylobacter* infections increased little until 1996-97, soon after the 1995 FDA approval of these drugs for use in poultry.[40] McDermott et al. (2002) have demonstrated that in poultry flocks given such fluoroquinolones, *Campylobacter* bacteria rapidly become less sensitive to these drugs, and the resistance persists long after the antibiotic is stopped.[41] In 2000, the FDA proposed banning these poultry fluoroquinolones, due to concern that their use has contributed to the dramatic rise in the prevalence of Cipro-resistant *Campylobacter* infections in humans.

Health Hazards from Resistant Bacteria on Retail Meats

There are no good estimates of how many people suffer from foodborne infections resistant to antibiotics. The Food and Drug Administration's best estimate using 1999 data is that 153,580 Americans developed FQ-resistant (Cipro-resistant) *Campylobacter* infections alone after eating contaminated chicken inside the U.S.[42] Most human infections with antibiotic-resistant *Salmonella* come from contaminated food, as well.[43,44,45,46,47]

While eating contaminated food may be the most obvious way to contract a resistant infection, bacteria in meat juices can also contaminate kitchen surfaces and utensils, indirectly leading to infection.

Though most infections do not require them, it is not uncommon for foodborne illness to be treated with antibiotics. Forty percent of patients with *Salmonella* seeking treatment received antibiotics, according to CDC surveys in 1990 and 1995. Rising antibiotic resistance among foodborne pathogens, like *Salmonella* and *Campylobacter*, therefore carries direct health consequences, a few of which are described.[48,49,50]

Less effective antibiotics, and fewer alternatives. Patients with bacterial infections respond poorly to an antibiotic given empirically (without a culture) if it turns out to be a medicine to which the bacteria are resistant.

Antibiotics work best at limiting the duration of a serious (bacterial) foodborne infection when taken early, even before cultures have confirmed exactly which microbe is the cause.[51,52] Yet, an infection caused by an actually resistant bacterial strain can mean that the initial, empirically-chosen antibiotic proves to be ineffective. Even a suspicion of resistance, therefore, can compel a health practitioner to choose a more toxic or

expensive antibiotic than would otherwise be the case. The rising resistance of foodborne pathogens to fluoroquinolones, therefore, is particularly concerning.[53]

Fluoroquinolone antibiotics, like Cipro, are currently favored for empirically treating a severe foodborne infection of undetermined origin, because they work against most bacterial causes and have relatively few side effects. Rising resistance among foodborne bacteria means that previously used medicines are no longer favored. Macrolide antibiotics (like erythromycin) are also effective for treating *Campylobacter*, but not *Salmonella* or many other foodborne pathogens, so they are less useful as an empiric therapy.

A recent Minnesota study found that sixty-five percent of patients treated for *Campylobacter* received a fluoroquinolone antibiotic. Fluoroquinolones are not approved for use in children, however.

Ciprofloxacin also is the most-prescribed antibiotic for *Salmonella* infections, according to CDC surveys.[54] Expanded spectrum cephalosporins are the current antibiotic of choice for treating children with serious *Salmonella* infection, in part due to the low prevalence of resistance. In the past, ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole (Bactrim) have all been the "drug of choice" for treating *Salmonella* infections.[55]

Increased resistance to any antibiotics used for treating severe foodborne infections is worrisome. Because they are the antibiotics of choice for serious infections in adults and children, however, increased *Campylobacter* resistance to erythromycin and fluoroquinolones, or *Salmonella* resistance to fluoroquinolones and cephalosporins, would have grave consequences for human health. Because of their beneficial properties, no clear and effective alternatives are available to these critical medicines.

Worse, more prolonged illness. For both *Salmonella* and *Campylobacter*, data suggest that antibiotic-resistant strains cause more severe or more prolonged illnesses than do non-resistant strains. For example, one recent study estimates that each year more than 400,000 additional days of diarrhea can be attributed to people in the U.S. contracting fluoroquinolone-resistant *Campylobacter* infections from domestically contaminated food.[56]

Not everyone is equally vulnerable to antibiotic-resistant infections. Children face higher risks, and more limited treatment options. Infants are ten times more likely than the general population to contract *Salmonella* infections, for example, and twice as likely as older people to suffer a *Campylobacter* infection.[57] Infants and toddlers also can become infected by lower levels of bacteria on food than do adults. In newborns and very young infants, such infections are more likely to invade the bloodstream.[58] With *Salmonella* and other foodborne pathogens becoming increasingly resistant to existing antibiotics, fewer medicines may be available to treat children with these infections.[59]

More infections. Foodborne pathogens need not be resistant to the antibiotics specifically used for treating foodborne disease for that resistance to be significant to public health.

The normal complement of bacteria in the human gut provides an important level of protection against intestinal infections by disease-causing bacteria. Even routine antibiotic use disrupts this protection, increasing a person's odds of getting an infection if exposed to a foodborne pathogen.

When that foodborne pathogen is resistant to an antibiotic (or more than one), however, studies suggest the person who happens to be taking that same medicine – even for an unrelated reason – has a more than 3-fold greater vulnerability to being infected.[60] In other words, antibiotic resistance among foodborne bacteria actually results in *more* people getting sick with foodborne infections than would have been the case without such resistance. In 2002, a published study estimates that the mere presence of *Salmonella* and *Campylobacter* strains resistant to at least one antibiotic will result in 29,300 additional human *Salmonella* infections and 17,600 additional *Campylobacter* infections each year.[61]

Concerns About "Opportunistic" Bacteria on Meat

The human intestine is colonized by around 500 commensal bacteria species.[62] Commensal bacteria typically cause no disease, but may do so opportunistically, when the immune system or other normal defenses against infection have been compromised – as in hospitalized patients, or patients undergoing chemotherapy for cancer. Some of these non-pathogenic bacteria are found on food, and are also becoming more and more resistant to antibiotics. They pose a health threat as well.

Enterococci bacteria are considered commensal. Retail meats are often contaminated with antibiotic-resistant *Enterococci*.[63,64,65] Danish researchers recently studied volunteers intentionally given chicken or pork contaminated with antibiotic-resistant *Enterococci*; these bacteria persisted in their intestines for at least two weeks.[66]

People whose intestines become colonized with drug-resistant *Enterococci* can later develop opportunistic infections in the hospital. Certain *Enterococci* strains, with resistance to vancomycin and with high-level resistance to gentamicin, have become important causes of illness and death in hospitals.[67] Gentamicin and vancomycin are important treatments for *Enterococci* infections; many strains resistant to these drugs may now only be treated with two newer human antibiotics, linezolid (Zyvox) and quinupristin/dalfopristin (Synercid). Synercid, a combination of two streptogramin antibiotics, was FDA-approved in 1999 specifically for treating these resistant infections. Resistance to Synercid is increasing however.

Gentamicin along with virginiamycin, a close cousin of Synercid, is frequently used non-therapeutically, for growth promotion and disease prevention in chickens. Research suggests the widespread use of virginiamycin and gentamicin in chickens has created a reservoir of Synercid-resistant and gentamicin-resistant *Enterococci* in the food supply.[68] This raises concerns that poultry contaminated with these bacteria may carry the "seeds" of resistance to these medicines from animals into the intestinal flora of the human populations, where *Enterococci* is also part of the normal bacterial flora.[69]

CHAPTER 3

PATHOGENS IN POULTRY: OUR TEST RESULTS

For this project, we bought and had tested chicken and turkey products routinely available to shoppers at large supermarket chains in Des Moines, Iowa and Minneapolis-St. Paul, Minnesota.

We tested 200 fresh whole chickens and 200 packages of fresh ground turkey in all, 100 of each from the two states. Iowa-purchased poultry products included Country Pride chicken and Honeysuckle White turkey; Minnesota-purchased brands were Gold'N Plump chicken and Jennie-O turkey. Each brand is commonly found in groceries, either regionally or nationally.

Gold'N Plump chicken is produced by Gold'N Plump Poultry (St. Cloud, MN). Country Pride is a brand of ConAgra Poultry Group (Duluth, GA). Ground turkey under the Jennie-O and Honeysuckle White labels are products of Jennie-O Turkey Store, Inc. (Willmar, MN) – a subsidiary of Austin, MN-based Hormel Foods, and Cargill, Inc. (Minneapolis, MN).

We contracted with a certified food-testing laboratory to test the products for the presence of three bacterial strains – *Salmonella*, *Campylobacter* and *Enterococci* – and for resistance to a number of antibiotics. For cost reasons, not every meat sample was tested for every type of bacteria (Table 2 and Tables A-2 and A-3 in Appendix A). Testing also was not done to determine the exact strain of certain bacteria present on the meat – *Salmonella typhimurium*, for example. Finally, not every bacteria actually isolated in these tests was itself tested for antibiotic resistance.

Table 2: Number of Whole Chickens and Ground Turkey Packages Tested for Prevalence of Bacteria

	Enterococcus	*Salmonella*	*Campylobacter*
Whole Chicken			
Gold'N Plump	50	100	50
Country Pride	50	100	50
Overall	100	200	100
Ground Turkey			
Jennie-O	50	100	50
Honeysuckle White	51	100	51
Overall	101	200	101

Appendix A describes in detail the methodology for collecting the meat samples, as well as the methodology for the actual testing of the meat samples. Appendix B summarizes the results of testing individual bacteria for resistance to antibiotics.

Whole Chicken Contamination

Laboratory testing found that, overall, nearly 18 percent of the fresh whole chickens purchased were contaminated with *Salmonella*, the second leading bacterial cause of foodborne illness in the U.S. (Table 3).

Table 3: Prevalence of Foodborne Pathogens on Whole Chicken, Ground Turkey Purchased in Minnesota and Iowa			
	Salmonella	***Campylobacter***	**Both**
Whole Chicken			
Gold'N Plump	15.0%	94.0%	14.0%
Country Pride	20.0%	96.0%	32.0%
Overall	17.5%	95.0%	23.0%
Ground Turkey			
Jennie-O	34.0%	2.0%	2.0%
Honeysuckle White	56.0%	2.0%	0.0%
Overall	45.0%	2.0%	1.0%

Twenty percent of Country Pride chickens carried *Salmonella*, as did 15 percent of Gold'N Plump chickens. By comparison, in 2001 the prevalence of *Salmonella* on whole chickens from large slaughter facilities passing the USDA's *Salmonella* "baseline" or standard under its HACCP inspection program was 9.7 percent – although this program tests chicken in the slaughterhouse, not at the retail level. The contamination rate in all slaughter facilities, large, small or very small, was 11.9 percent.[70] Both of the chicken brands we tested exceeded these levels.

All 35 *Salmonella* isolated from whole chickens were analyzed for antibiotic resistance. Nearly six percent (n=2) were resistant to 4 or more antibiotics (Table 4). One of these *Salmonella*, from a Gold'N Plump chicken, carried resistance to gentamicin, streptomycin, sulfamethoxazole, and tetracycline. The other, from a Country Pride chicken, was resistant to six antibiotics, including augmentin-clavulinic acid, ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline. Though no resistance to Cipro was observed in these *Salmonella* from chicken, there was some resistance to ampicillin and chloramphenicol, which – along with trimethoprim-sulfamethoxazole (Bactrim) – have been "treatments of choice" for Salmonella infections in the past.[71]

Table 4: *Salmonella* Resistance to One or Multiple Antibiotics (in % of isolates tested)					
	1 or more	**2 or more**	**3 or more**	**4 or more**	**5 or more**
Whole Chicken					
Gold'N Plump	6.7%	6.7%	6.7%	6.7%	0.0%
Country Pride	5.0%	5.0%	5.0%	5.0%	5.0%
Overall	5.7%	5.7%	5.7%	5.7%	2.9%
Ground Turkey					
Jennie-O	58.8%	58.8%	58.8%	58.8%	5.9%
Honeysuckle White	64.3%	42.9%	42.9%	14.3%	7.1%
Overall	62.2%	48.9%	48.9%	31.1%	6.7%

Campylobacter contaminated 95 percent of the whole chickens tested.

Forty-seven of the *Campylobacter* found on chicken were further tested for resistance. Nearly 62 percent (n=29) were found resistant to 1 or more antibiotics, and more than 6 percent (n=3) were resistant to 2 or more antibiotics (Table 5).

More than 6 percent of these chicken isolates overall were resistant to Cipro. By brand, 8.7 percent (2 isolates) of *Campylobacter* on Country Pride chickens, and 4.2 percent (1 isolate) on Gold'N Plump chickens, were Cipro-resistant (Appendix B).

Table 5: *Campylobacter* Resistance to One or Multiple Antibiotics (in % of isolates tested)

	1 or more	2 or more	4 or more
Whole Chicken			
Gold'N Plump	75.0%	4.2%	0.0%
Country Pride	47.8%	8.7%	4.3%
Overall	61.7%	6.4%	2.1%
Ground Turkey			
Jennie-O	100.0%	100.0%	100.0%
Honeysuckle White	100.0%	0.0%	0.0%
Overall	100.0%	50.0%	50.0%

Ground Turkey Contamination

Ground turkey tested was more contaminated with *Salmonella* than was whole chicken, with an overall rate of 45 percent. Fifty-six percent of Honeysuckle White turkey carried *Salmonella* bacteria, while contamination of Jennie-O turkey, at 34 percent, was somewhat lower.

By comparison, in 2001 the prevalence of *Salmonella* in ground turkey from large slaughter facilities passing the USDA's *Salmonella* "baseline" or standard under its HACCP inspection program was 25.2 percent. Again, ground turkey that we tested of either brand exceeded this level. *Salmonella* contamination of Honeysuckle White turkey was more than twice as high.

Of the 90 *Salmonella* isolated from ground turkey overall, half were tested for antibiotic resistance. Over 62 percent (28 of 45) of the latter were resistant to at least one antibiotic, almost half were resistant to 3 or more antibiotics, and roughly one-third to 4 or more antibiotics (Table 4). Resistant turkey isolates were most likely to carry resistance to the antibiotics streptomycin and tetracycline (48.9 percent), sulfamethoxazole (42.2 percent) and gentamicin (35.6 percent). Kanamycin resistance was 15.6 percent (Table 6).

While the Jennie-O products tested carried less *Salmonella* than did Honeysuckle White products, the resistant *Salmonella* in the Jennie-O products tended to be resistant to more antibiotics; nearly 59 percent of these isolates were resistant to four or more antibiotics, compared with just over 14 percent for Honeysuckle White.

Table 6: Antibiotic Resistance Summary for 35 *Salmonella* Isolates from Chicken, 45 Isolates from Turkey		
	Whole Chicken	Ground Turkey
Antibiotic	% Resistant	% Resistant
Amikacin	0.0%	0.0%
Amoxicillin-clavulanic acid	2.9%	2.2%
Ampicillin	2.9%	0.0%
Cefoxitin	0.0%	2.2%
Ceftiofur	0.0%	0.0%
Ceftriaxone	0.0%	0.0%
Cephalothin	0.0%	2.2%
Chloramphenicol	2.9%	0.0%
Ciprofloxacin	0.0%	0.0%
Gentamicin	2.9%	35.6%
Kanamycin	0.0%	15.6%
Nalidixic acid	0.0%	0.0%
Streptomycin	5.7%	48.9%
Sulfamethoxazole	5.7%	42.2%
Tetracycline	5.7%	48.9%
Trimethoprim-sulfamethoxazole	0.0%	0.0%

Of the two *Campylobacter* isolated from ground turkey packages, both were antibiotic resistant. One, from a Jennie-O package, was the most resistant of any *Campylobacter* bacteria identified, with resistance to six antibiotics including ciprofloxacin (Cipro), tetracycline and erythromycin. The same package also yielded a *Salmonella* bacterium resistant to four antibiotics.

Cipro and erythromycin are the two antibiotics of choice for treating severe *Campylobacter* infections in adults, so the presence of bacteria resistant to both of them raises concerns.

More than 8 percent of the *Campylobacter* isolated from chicken or turkey products and tested for resistance were resistant to Cipro (Table 7), while more than 61 percent were resistant to tetracycline. Only the turkey *Campylobacter* isolate mentioned above was fully resistant to erythromycin. In 22 percent of the *Campylobacter* bacteria tested, however, there was diminished susceptibility to erythromycin, meaning they were somewhat resistant. Whether or not this has implications for the likely evolution of full resistance to erythromycin in the future is unclear.

Table 7: Antibiotic Resistance Summary for 49 *Campylobacter* Isolates from Poultry		
Antibiotic	% Resistant	% Intermediate
Azithromycin	2.0	12.2
Chloramphenicol	0.0	0.0
Ciprofloxacin	8.2	0.0
Clindamycin	2.0	14.3
Erythromycin	2.0	22.4
Gentamicin	0.0	2.0
Nalidixic acid	8.2	0.0
Tetracycline	61.2	0.0

In 2001, the Union of Concerned Scientists estimated that 1.4 million pounds of a tetracycline antibiotic (chlortetracycline), and 380,000 pounds of erythromycin, annually are fed to poultry flocks for non-therapeutic purposes.[72]

***Enterococcus* Contamination.** *Enterococcus* was found on 100% of the chicken and turkey products we tested from Iowa and Minnesota. *Enterococcus* is a group of approximately twenty species of bacteria that are ubiquitous in man, animals and in the environment. In healthy persons, *Enterococci* are considered benign. In hospitals, however, antibiotic-resistant strains are becoming an important cause of serious, difficult-to-treat infections. We did not attempt to identify particular species of *Enterococci*.

Table 8: *Enterococci* Resistance to One or Multiple Antibiotics (in % of isolates tested)

	1 or more	2 or more	3 or more	4 or more	5 or more
Whole Chicken					
Gold'N Plump	100.0%	92.0%	60.0%	32.0%	4.0%
Country Pride	96.0%	56.0%	16.0%	4.0%	0.0%
Overall	98.0%	74.0%	38.0%	18.0%	2.0%
Ground Turkey					
Jennie-O	100.0%	88.0%	16.0%	0.0%	0.0%
Honeysuckle White	100.0%	100.0%	19.2%	0.0%	0.0%
Overall	100.0%	94.1%	17.6%	0.0%	0.0%

Of the 100 *Enterococci* bacteria isolated from whole chickens, half were tested for antibiotic resistance. Ninety-eight percent (n=49) of those were found resistant to one or more antibiotics, nearly 75 percent to two or more antibiotics (n=37), and 38 percent (n=19) to 3 or more antibiotics. Almost one in five *Enterococci* carried resistance to 4 or more antibiotics (Table 8). Gold'N Plump whole chickens carried a higher percentage of *Enterococci* bacteria resistant to 3 or more antibiotics at 60 percent (n=15), and to 4 or more antibiotics at 32 percent (n=8), than did other whole chicken or ground turkey brands.

Table 9: Antibiotic Resistance Summary for 101 Enterococci Isolates from All Whole Chicken and Ground Turkey Products

Antibiotic	% Resistant
Chloramphenicol	1.0
Ciprofloxacin	1.0
Erythromycin	19.8
Gentamicin	10.9
Linezolid	0.0
Nitrofurantoin	0.0
Penicillin	1.0
Quinupristin/dalfopristin	96.0
Streptomycin	8.9
Tetracylcine	81.2
Vancomycin	0.0

For all 101 *Enterococci* isolated from chicken or turkey products and subsequently tested for resistance (Table 9), resistance was most likely to quinupristin/dalfopristin (96 percent), tetracycline (81.2 percent), erythromycin (19.8 percent), and gentamicin (10.9 percent). Resistance to Synercid was somewhat higher for bacteria from turkey versus chicken (100% to 92%), as was also true for tetracycline (92% versus 70%). The reverse, higher resistance in chicken versus turkey isolates, was true for erythromycin (32% to 8%) and gentamicin (18% to 4%).

CHAPTER 4

CONCLUSION AND RECOMMENDATIONS

For decades, antibiotics have dramatically reduced illness and death from bacterial infections. But recently, the effectiveness of these life-saving drugs has begun to wane because antibiotics are being overused.

Antibiotic overuse is the key factor in development of antibiotic resistance. Certainly, antibiotics are being overused in human medicine. But industrial-scale poultry producers also routinely put antibiotics in poultry feed, more than 10 million pounds a year by some estimates. More than 2 million pounds per year are antibiotics identical or closely related to important human medicines.

Evidence now links the widespread use of antibiotics in animal feed with the transmission to humans of antibiotic-resistant bacteria, and an increase in antibiotic-resistant infections that respond less well to treatment with these same, or similar, medicines.[73,74,75,76,77] In 1989, the Institute of Medicine estimated that as much as 90 percent of drug-resistant *Salmonella* in food stems from the practice of giving antibiotics to food animals at lower than therapeutic levels.[78]

The American Medical Association has gone on record opposing the use of antibiotics in farm animals that aren't sick. Other medical professionals are also speaking out. If they cannot rely upon these antibiotics, it will become more difficult and in some cases impossible to treat bacterial illnesses.

This report, based on testing of 400 poultry products purchased in Des Moines and Minneapolis-St. Paul, finds these products were frequently contaminated with bacteria that can cause infections. In this respect, our study confirms data available from previous government surveys and other studies (Table 10).

Table 10: *Campylobacter* and *Salmonella* on Retail and Slaughterhouse Whole Chicken and Ground Turkey: A Comparison of Findings from Several Studies

	Whole Chicken		Ground Turkey	
Study	*Campylobacter*	*Salmonella*	*Campylobacter*	*Salmonella*
FSIS, 1994-95	88.2%	20.0%	25.4%	49.9%
Smith et al. (MN) 1997*	87.9%			
White et al., 2001				24.0%
HACCP Baseline	NA	20.0%	NA	49.9%
HACCP 2001**	NA	9.7%	NA	25.2%
IATP/Sierra Club (MN & IA) 2002	96.0%	17.5%	2.0%	45.0%

* Tested "retail chicken products" and not whole chickens, necessarily.
** Prevalence of contamination in poultry from large facilities passing HACCP standards

Our tests also revealed, however that the bacteria on these products frequently were resistant to one or multiple antibiotics important to human medicine, like Cipro, gentamicin and Synercid. In one case, the same package of ground turkey carried multiple pathogenic bacteria, each resistant to multiple human antibiotics.

Among the *Campylobacter* found on poultry and tested, over 8 percent were resistant to Cipro – which, along with closely related drugs, are the antibiotics that doctors most rely upon for treating Campylobacter infections, as well as other severe, potentially life-threatening cases of food poisoning in adults. In 2000, the FDA concluded that continued use of the Cipro analog, Baytril (enrofloxacin) in poultry flocks makes Cipro less effective for treating people sick with severe cases of *Campylobacter* food poisoning. The agency estimated that in 1999, the eating of chickens contaminated with fluoroquinolone (FQ)-resistant *Campylobacter* bacteria led to 153,580 Americans developing a foodborne infection caused by FQ-resistant bacteria. FDA's best estimate was that 9,261 of these sick people subsequently were given Cipro, or a related medicine, to try and treat their infection.[79]

Subsequently, the FDA proposed banning the use of FQ antibiotics like Baytril on poultry. One manufacturer, Abbott Laboratories, complied with this request. Another, Bayer, has refused. Bayer continues to manufacture the drug, and poultry companies continue to use it. Bayer should voluntarily withdraw the use of this product to protect public health.

The widespread resistance of *Enterococci* found in our testing of both chicken and turkey products is another concern, especially the near universal resistance to Synercid. Synercid has only been used in people since 1999, while its close analog, virginiamycin, has been used non-therapeutically in poultry since 1974. Since resistant *Enterococci* from food can persist in the human intestine for weeks, there is grave concern that there will be rising Synercid-resistant infections in people, as rising human use of the medicine creates the conditions for these originally foodborne, Synercid-resistant bacteria to propagate and cause increased infections in humans.

Recommendations

Consumers expect the meat they purchase to be free of health-threatening bacteria. Increasingly, though, we have learned that food products, particularly meats, may be contaminated with bacteria that pose serious health risks.

The science clearly shows that raising animals with antibiotics results in antibiotic-resistant bacteria that get transmitted to people, typically via the eating of food contaminated with them. It stands to reason that chicken and turkeys raised without antibiotics are less likely to carry resistant bacteria.

Industry, consumers and government therefore all should act to reduce the threat of antibiotic-resistant bacteria in food.

Consumers can help reduce the threat simply by buying chicken or turkey raised without antibiotics, or at the very least, without antibiotic growth promoters or other non-therapeutic antibiotics. By choosing these products, consumers also are supporting producers who raise poultry using methods less likely to introduce resistant bacteria – and the genes that make them resistant – into the broader environment, including surface waters, groundwater and soil.

Poultry produced with little or no antibiotics is widely available throughout the U.S. One certain way of buying it is to purchase certified organic chickens and turkeys. Other producers, particularly smaller ones, may claim to use no antibiotics even if they have not gone through the expense of becoming certified organic.

Consumers can buy poultry products, for example, carrying "raised without antibiotics" or "no antibiotics administered" on the label, which the USDA defines as meaning meat from animals receiving no antibiotics over the course of their lifetime. Since USDA does define the terms, it has authority to hold producers responsible for the use of these labels. Unlike certified organic meats, however, neither USDA nor any independent, third party verifies the claims.[80]

Check the **Eat Well Guide**, *www.iatp.org/EatWell*, for a state-by-state listing of organic and other meat and poultry producers using either no antibiotics, or no routine antibiotics, in addition to restaurants and other places to buy these products.

Whatever meat products consumers purchase, they should always practice safe meat handling procedures. This will help avoid contamination between or on food items, cooking utensils, countertops, and other kitchen surfaces. Consumer advice is available at the website, *www.foodsafety.gov*.

Some industry groups also have begun to take some steps to address this problem. McDonald's, Popeye's and Wendy's all now state it is their policy not to buy chicken from producers using Cipro-like antibiotics.[81] Several other fast food companies, like Hardee's, Subway and Domino's, have similar policies, but also say they will not buy chickens fed important human antibiotics for non-therapeutic reasons, like growth promotion.[82]

Four of the top five top chicken producers also have sworn off any use of Cipro-like antibiotics, including ConAgra Poultry, producers of Country Pride chicken. Others, also including ConAgra, claim to have stopped using or to have greatly reduced the use of antibiotics for growth promotion or disease prophylaxis. We generally laud this approach, although there is no mechanism for verifying producers' claims.

While these are promising initial steps, all poultry producers should commit to reducing overall antibiotic use to a minimum, and to phasing out the use of antibiotics in animals that are not even sick. This especially includes ending the non-therapeutic use of antibiotics that are, or may become, important to human medicine.

Drug manufacturers also have a part to play in protecting the effectiveness of antibiotics for the benefit of everyone. And yet the failure of Bayer to act responsibly in withdrawing its Cipro-like product from the poultry market highlights the need for strong governmental action.

As a priority, the FDA should ban the use of fluoroquinolone antibiotics in poultry, as it has proposed. Two years have already passed since FDA first launched its proposal. Fluoroquinolones are critical antibiotics for treating many infections, including severe cases of food poisoning. FDA needs to act quickly lest this critical human drug lose any more of its effectiveness for treating seriously ill people.

ENDNOTES

1 Associated Press, "Largest Meat Recall in U.S. History Announced," (October 14, 2002).

2 Mead PS, L Slutsker, V Dietz, LF McCaig, JS Bresee, C Shapiro, PM Griffini, and RT Tauxe. Food-related illness and death in the United States. Emerg Infect Dis **5**:607-625 (1999). *http://www.cdc.gov/ncidod/EID/vol5no5/pdf/mead.pdf*

3 Ibid.

4 Ibid.

5 Ibid.

6 Angulo F, K Johnson, R Tauxe, and M Cohen. Significance and sources of antimicrobial-resistant nontyphoidal Salmonella infections in the United States, Microbial Drug Resistance. **6(1)**: 77-83 (2000).

7 Smith K, et al. Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992 –1998. NEJM **340**:1525-1532 (1999).

8 U.S. Food and Drug Administration, Center for Veterinary Medicine. The Human Health Impact of Fluoroquinolone Resistant Campylobacter Attributed to the Consumption of Chicken. Washington, DC, January 5, 2001. *http://www.fda.gov/cvm/antimicrobial/revisedRA.pdf.*

9 US Department of Agriculture, Food Safety Inspection Service, Science and Technology Microbiology Division. Nationwide broiler chicken microbiological baseline data collection program, July 1994-June 1995. Washington, DC: US Department of Agriculture, 1996. *http://www.fsis.usda.gov/OPHS/baseline/contents.htm.*

10 Angulo F, K Johnson, R Tauxe, and M Cohen. Significance and sources of antimicrobial-resistant nontyphoidal Salmonella infections in the United States, Microbial Drug Resistance. **6(1)**: 77-83 (2000).

11 Swartz MN. Human diseases caused by foodborne pathogens of animal origin. Clin Infect Dis **34** (Suppl 3): S111-22 (2002).

12 Angulo F, K Johnson, R Tauxe, and M Cohen. Significance and sources of antimicrobial-resistant nontyphoidal Salmonella infections in the United States, Microbial Drug Resistance. **6(1)**: 77-83 (2000).

13 Smith K, et al. Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992 –1998. NEJM **340**:1525-1532 (1999).

14 Travers K and M Barza. Morbidity of infections caused by antimicrobial-resistant bacteria. Clin Infect Dis **34** (Suppl 3): S131-4 (2002).

15 Barza M , SL Gorbach, Eds. The need to improve antimicrobial use in agriculture: ecological and human health consequences. Clin Infect Dis **34** (Suppl 3):S71-144 (2002). http://www.journals.uchicago.edu/CID/journal/contents/v34nS3.html. Accessed November 30, 2002.

16 Gorbach SL (editorial). Antimicrobial use in animal feed – time to stop. NEJM **345(16)**:1202-03 (2001).

17 Falkow S and D Kennedy (editorial). Antibiotics, animals, and people—again! Science **291**:397 (2001).

18 World Health Organization, Department Of Communicable Disease Surveillance And Response, WHO Global Principles For The Containment Of Antimicrobial Resistance In Animals Intended For Food: Report of a WHO Consultation with the participation of the Food and Agriculture Organization of the United Nations and the Office International des Epizooties, Geneva, Switzerland, 5-9 June 2000.

19 Angulo F, K Johnson, R Tauxe, and M Cohen. Significance and sources of antimicrobial-resistant nontyphoidal Salmonella infections in the United States, Microbial Drug Resistance. **6(1)**: 77-83 (2000).

20 Witte W. Medical consequences of antibiotic use in agriculture. Science **279**:996-7 (1998).

21 Tollefson L, SF Altekruse, ME Potter. Therapeutic antibiotics in animal feeds and antibiotic resistance, Rev Sci Tech **16**:709-15 (1997).

22 Mellon M and S Fondriest. Union of Concerned Scientists. Hogging it: estimates of animal abuse in livestock. Nucleus 23:1-3 (2001). *http://www.ucsusa.org*, by choosing "antibiotic resistance" and choosing report for right-hand menu. Accessed Aug. 28,2002.

23 Carnevale R, Presentation to the US Animal Health Association, November 2001; accessed on the website of the Animal Health Institute, www.ahi.org, November 27, 2002.

24 Chapman HD and ZB Johnson. Use of Antibiotics and Roxarsone in Broiler Chickens in the USA: Analysis for the Years 1995 to 2000, Poultry Science **81**:356-364 (2000).

25 Copeland C and J Zinn. Animal Waste Management and the Environment: Background for Current Issues, Report for Congress, Washington, D.C.: Congressional Research Service, 1998.

26 Ibid.

27 Chapman HD and ZB Johnson. Use of Antibiotics and Roxarsone in Broiler Chickens in the USA: Analysis for the Years 1995 to 2000, Poultry Science **81**:356-364 (2000). Note: the industry database defines a poultry "plant" as a production unit in most cases representing a broiler complex comprising a group of individual farms, in a common geographical area, served by a single feed mill.

28 Ibid.

29 Mellon M and S Fondriest. Union of Concerned Scientists. Hogging it: estimates of animal abuse in livestock. Nucleus 23:1-3 (2001). *http://www.ucsusa.org*, by choosing "antibiotic resistance" and choosing report for right-hand menu. Accessed Aug. 28,2002.

30 Ibid.

31 Carnevale R, Presentation to the US Animal Health Association, November 2001; accessed on the website of the Animal Health Institute, *www.ahi.org*, November 27, 2002.

[32] US Department of Agriculture, Food Safety Inspection Service, Science and Technology Microbiology Division. Nationwide broiler chicken microbiological baseline data collection program, July 1994-June 1995. Washington, DC: US Department of Agriculture, 1996. Internet: *http://www.fsis.usda.gov/OPHS/baseline/contents.htm.*

[33] US Department of Agriculture, Food Safety Inspection Service, Science and Technology Microbiology Division. Nationwide raw ground turkey microbiological survey. Washington, DC: US Department of Agriculture, May 1996. Internet: *http://www.fsis.usda.gov/OPHS/baseline/contents.htm.*

[34] US Department of Agriculture, Food Safety Inspection Service, Progress Report on Salmonella Testing of Raw Meat and Poultry Products, 1998-2001, accessed December 1, 2002 at: *http://www.fsis.usda.gov/OPHS/haccp/salm4year.htm.*

[35] Center for Science in the Public Interest, Field Guide to Safer Turkeys, accessed November 22, 2002 at *www.cspinet.org/new/200211211.htm.*

[36] White DG, S Zhao, and R Sudler, et al. The isolation of antibiotic-resistant Salmonella from retail ground meats. N Engl J Med **345**:1147-54 (2001).

[37] Ibid.

[38] Smith K, et al. Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992 –1998. NEJM **340**:1525-1532 (1999).

[39] Preliminary data from the Centers for Disease Control and Prevention, National Antimicrobial [Antibiotic] Resistance Monitoring System for Human Enteric Bacteria:Summary: Antimicrobial [Antibiotic] Resistance of *Campylobacter* isolates, 1997-2001, Presented at the National Antimicrobial [Antibiotic] Resistance Monitoring Systems 2002 Annual Scientific Meeting in Hilton Head Island, SC, November 20, 2002.

[40] U.S. Department of Health and Human Services, Food and Drug Administration (FDA), "Enrofloxacin for Poultry; Opportunity for Hearing," 65 FR 64954-64965 (October 31, 2000).

[41] McDermott PF, SM Bodels, LL English, et al. Ciprofloxacin resistance in *Campylobacter jejuni* evolves rapidly in chickens treated with fluoroquinolones. JID **185**: 837-40 (2002).

[42] Department of Health and Human Services, Food and Drug Administration. Enrofloxacin for Poultry; Opportunity for Hearing; Correction. 66 FR 6623-6624 (January 22, 2001).

[43] MMWR Weekly, Outbreak of multidrug-resistant *Salmonella newport* --- United States, January—April 2002. **51(25)**:545-548 (June 28, 2002).

[44] Chiu C-H, T-L Wu, L-H Su, et al. The emergence in Taiwan of fluoroquinolone resistance in *Salmonella enterica* serotype choleraesuis. NEJM **346**:413-19 (2002).

[45] Angulo F, K Johnson, R Tauxe, and M Cohen. Significance and sources of antimicrobial-resistant nontyphoidal Salmonella infections in the United States, Microbial Drug Resistance. **6(1)**: 77-83 (2000).

[46] Molbak K, DL Baggesen, FM Aarestrup, et al. An outbreak of multidrug-resistant, quinolone-resistant *Salmonella enterica* serotype typhimurium DT104. NEJM **341**:1420-5 (1999).

[47] Holmberg SD, MT Ostereholm, KA Senger, and ML Cohen. Drug-resistant Salmonella from animals fed antimicrobials. NEJM **311**:617-22 (1984).

[48] Swartz MN. Human diseases caused by foodborne pathogens of animal origin. Clin Infect Dis **34** (Suppl 3): S111-22 (2002).

[49] Angulo F, K Johnson, R Tauxe, and M Cohen. Significance and sources of antimicrobial-resistant nontyphoidal Salmonella infections in the United States, Microbial Drug Resistance. **6(1)**: 77-83 (2000).

[50] Smith K, et al. Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992 –1998. NEJM **340**:1525-1532 (1999).

[51] McDermott PF, SM Bodels, LL English, et al. Ciprofloxacin resistance in *Campylobacter jejuni* evolves rapidly in chickens treated with fluoroquinolones. JID **185**: 837-40 (2002).

[52] Mattila L, H Peltola, A Siitonen, H Kyronseppa, I Simula, M Kataja. Short-term treatment of traveler's diarrhea with norfloxacin: a double-blind, placebo-controlled study during two seasons. Clin Infect Dis **17**:779-82 (1993).

[53] Dunne EF, PD Fey, P Kludt, et al. Emergence of Domestically acquired ceftriaxone-resistant Salmonella infections associated with AmpC β-lactamase. JAMA **284**:3151-56 (2000).

[54] Angulo F, K Johnson, R Tauxe, and M Cohen. Significance and sources of antimicrobial-resistant nontyphoidal Salmonella infections in the United States, Microbial Drug Resistance. **6(1)**: 77-83 (2000).

[55] Ibid.

[56] Travers K and M Barza. Morbidity of infections caused by antimicrobial-resistant bacteria. Clin Infect Dis **34** (Suppl 3): S131-4 (2002).

[57] USDA Report to Congress, "FoodNet: An Active Surveillance System for Bacterial Foodborne Diseases in the United States" (1998) *www.fsis.usda.gov/OPHS/rpcong09/rpcong98.htm.*

[58] T.B. Cleary, "Salmonella," in *Nelson Textbook of Pediatrics*, 16th ed., eds. RE Behrman, RM Kliegman, HB Jenson Philadelphia: Saunders, 842-48 (2000).

[59] Shea K, K Florini, and T Barlam. When Wonder Drugs Don't Work: How Antibiotic Resistance Threatens Children, Seniors, and the Medically Vulnerable, Environmental Defense: Washington, D.C. (2001). *http://www.environmentaldefense.org/documents/162_ABRreport.pdf.*

[60] Barza M and K Travers. Excess infections due to antimicrobial resistance: the "attributable fraction". CID **34**(Suppl 3):126-130 (2002).

[61] Barza M and K Travers. Excess infections due to antimicrobial resistance: the "attributable fraction". CID **34**(Suppl 3):126-130 (2002).

62 Swartz MN. Human diseases caused by foodborne pathogens of animal origin. Clin Infect Dis **34** (Suppl 3): S111-22 (2002).

63 Sorenson TL, M Blom, DL Monnett, N Frimodt-Moller, RL Poulsen, and F Espersen. Transient intestinal carriage after ingestion of antibiotic-resistant *Enterococcus faecium* from chicken and pork. NEJM **345**:1161-6 (2001).

64 Mcclellan J, K Joyce, S Rossiter, T Barrett, and F Angulo. High-level Gentamicin resistant enterococci and quinupristin/dalfopristin resistant E. faecium from ground pork purchased from grocery stores. The 41rst Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) annual meeting. Chicago, IL 2001. Accessed at: *http://www.cdc.gov/narms/pub/presentations/icaac/2001/mcclellan_j.htm.*

65 McDonald LC, S Rossiter, C Mackinson, et al. Quinipristin-dalfopristin-resistant *Enterococcus faecium* on chicken and in human stool specimens. NEJM **345**:1155-60 (2001).

66 Sorenson TL, M Blom, DL Monnett, N Frimodt-Moller, RL Poulsen, and F Espersen. Transient intestinal carriage after ingestion of antibiotic-resistant *Enterococcus faecium* from chicken and pork. NEJM **345**:1161-6 (2001)..

67 Angulo F, N Marano, S Johnson, C Mackinson, L Gilbert, M Park, E Debess, B Taylor, J Madden, B Hill, K Joyce, F Tenover, and L Archibald. EIP enterococci study: monitoring for the seeds of antimicrobial resistance in the food supply. Presentation to the 2nd International Conference on Emerging Infectious Diseases, Atlanta, GA, July 2000. *http://www.cdc.gov/narms.*

68 McDonald LC, S Rossiter, C Mackinson, et al. Quinipristin-dalfopristin-resistant *Enterococcus faecium* on chicken and in human stool specimens. NEJM **345**:1155-60 (2001).

69 Angulo F, K Johnson, R Tauxe, and M Cohen. Significance and sources of antimicrobial-resistant nontyphoidal Salmonella infections in the United States, Microbial Drug Resistance. **6(1)**: 77-83 (2000).

70 U.S. Department of Agriculture, Food Safety and Inspection Service, Progress Report on Salmonella Testing of Raw Meat and Poultry Products, 1998-2001, accessed 11/25/02 at: *http://www.fsis.usda.gov/OPHS/haccp/salm4year.htm*

71 Angulo F, K Johnson, R Tauxe, and M Cohen. Significance and sources of antimicrobial-resistant nontyphoidal Salmonella infections in the United States, Microbial Drug Resistance. **6(1)**: 77-83 (2000).

72 Mellon M and S Fondriest. Union of Concerned Scientists. Hogging it: estimates of animal abuse in livestock. Nucleus 23:1-3 (2001). *http://www.ucsusa.org,* by choosing "antibiotic resistance" and choosing report for right-hand menu. Accessed Aug. 28,2002.

73 Angulo F, K Johnson, R Tauxe, and M Cohen. Significance and sources of antimicrobial-resistant nontyphoidal Salmonella infections in the United States, Microbial Drug Resistance. **6(1)**: 77-83 (2000).

74 Dunne, EF, PD Fey, P Kludt, R Reporter, F Mostashari, P Shillam, J Wickland, C Miller, B Holland, K Starney, TJ Barrett, FC Tenover, E Ribot, and FJ Angulo. Emergence of domestically acquired ceftriaxone-resistent Salmonella infections associated with ampc B-lactamase. JAMA **284**: 3151-3156 (2000).

75 Federal Register, Enrofloxican for Poultry; Opportunity for Hearing, 64954-64965 (October 31, 2000).

76 Fey, PD, TJ Safranek, ME Rupp, EF Dunne, E Ribot, PC Iwen, PA Bradford, FJ Angulo and SH Hinrichs. Ceftriaxone-resistant salmonella infection acquired by a child from cattle. NEJM **342**: 1242-1249 (2000).

77 Levy, SB, GB Fitzgerald, and AB Macone. Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm. NEJM **295(11)**: 583-588 (1976).

78 Institute of Medicine. Human health risks with the subtherapeutic use of penicillin or tetracycline in animal feeds. National Academy Press. 1989.

79 Department of Health and Human Services, Food and Drug Administration. Enrofloxacin for Poultry; Opportunity for Hearing; Correction. 66 FR 6623-6624 (January 22, 2001).

80 For more information on USDA-defined labels, see www.eco-label.org.

81 Burros M, "Poultry Industry Quietly Cuts Back on Antibiotic Use," The New York Times (February 10, 2002).

82 Recent Statements on Antibiotic Use by Major Restaurant Chains, Compiled by Keep Antibiotics Working as of October 1, 2002, accessed November 25, 2002 at: *http://www.iatp.org/antibiotics/library/uploadedfiles/Recent_Statements_on_Antibiotic_Use_by_Major_R.htm*

Ban Antibiotics In Poultry?

[Why The Policymakers Have It Wrong]

Banning the use of certain antibiotics in poultry may increase the risk of foodborne illness. by Scott M. Russell

© Eyewire Images

The National Advisory Committee on Microbiological Criteria for Foods (NACMCF, 1997) reported that because processing of raw broilers does not involve a lethal heat process, such as pasteurization, delivering live chickens to the processing plant with as few pathogens as possible is necessary to control contamination of carcasses with salmonella and campylobacter. Other scientists have supported this conclusion by stating that reducing *C. jejuni* colonization in live chickens should reduce the prevalence of *C. jejuni* infections in humans, presumably because of less exposure to the organism (Morishita *et al.*, 1997). Controlling factors that contribute to colonization of the live bird during grow-out should significantly impact contamination of finished carcasses after processing.

At the processing plant, fecal contamination of carcasses can become a concern if the digestive tracts of chickens are cut or torn during venting, opening or evisceration because, if cut or torn, fecal material may be released onto the surface of the carcass (NACMCF, 1997). Intestinal damage is generally associated with improperly adjusted or worn-out evisceration equipment, variance among individual birds or birds with low body weight due to disease. These factors must be controlled because modern poultry processing plants are highly automated operations, and the equipment is set to receive carcasses of a specific size. Preventing contamination of carcasses from spillage of digestive tract contents or smearing of fecal material on edible meat surfaces is perhaps the single most important factor in sanitary poultry slaughter (Bilgili, 2001). If intestines are cut or torn during evisceration, feces can spread to equipment, workers and inspectors, and this can be a major source of cross-contamination with pathogenic bacteria (NACMCF, 1997).

Pilot studies conducted in 1997 by two vertically integrated broiler companies revealed a direct relation-

ship between air sacculitis infections in chickens and the presence of high numbers of *Escherichia coli* and salmonella. In the first study, carcasses that were removed from the line by USDA-FSIS inspectors for active air sacculitis infections, and carcasses that were not visibly infected were evaluated for *E. coli* counts over a one-week period (unpublished data). For carcasses with no visible signs of air sacculitis, 58 percent had pre-chill *E. coli* numbers in the acceptable range (0 to < 100 CFU/mL) according to the HACCP regulation (USDA-FSIS, 1996), 37 percent were found to be in the questionable range (100 to 1,000 CFU/mL), and only 5 percent were in the unacceptable range (> 1,000 CFU/mL). However, for carcasses removed from the line for air sacculitis infections, 4 percent, 46 percent and 50 percent of the pre-chill carcasses were in the acceptable, questionable and unacceptable ranges, respectively. Therefore, a total of 96 percent of air sacculitis-infected carcasses had questionable or unacceptable *E. coli* counts. In a second study conducted by another integrator, pre-chill *E. coli* counts for carcasses with air sacculitis were significantly higher ($P \leq 0.05$) at 3.93 $\log_{10}$ CFU/mL than air sacculitis-negative carcasses at 2.63 $\log_{10}$ CFU/mL. Moreover, this company found that salmonella prevalence for carcasses with air sacculitis was significantly higher ($P < 0.05$) at 70 percent than for carcasses without air sacculitis at 40 percent (unpublished data). These studies demonstrate a link between the presence of air sacculitis in the flock and increases in indicator and pathogenic bacterial populations.

Figure 1. The Effect Of Air Sacculitis On Carcass Weight And Uniformity

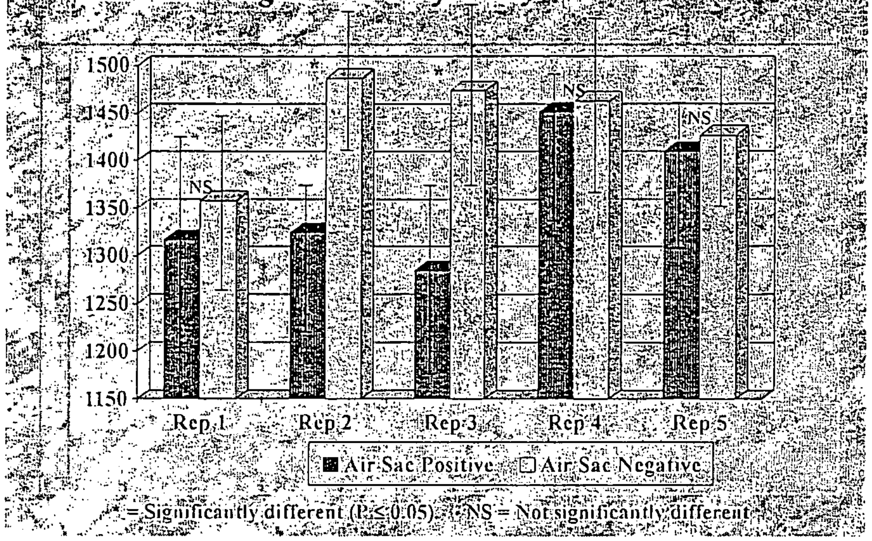
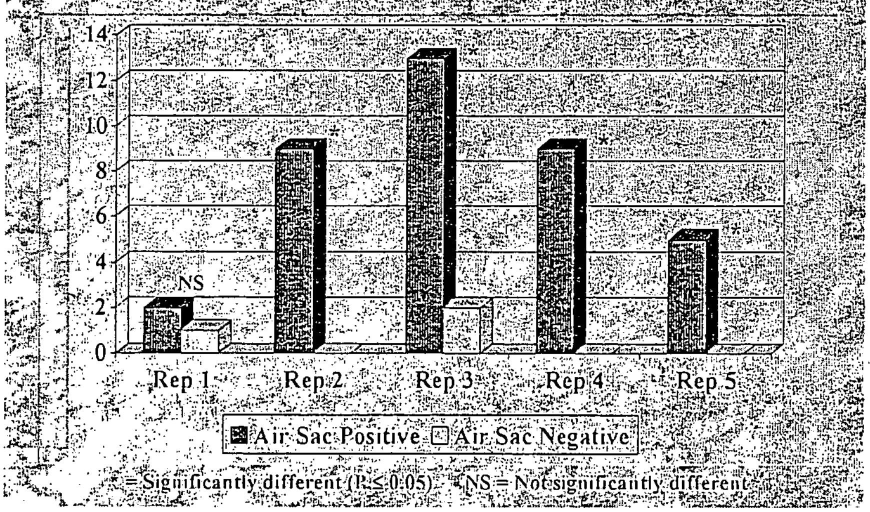


Figure 2. The Effect Of Air Sacculitis On Carcass Fecal Contamination



Georgia Study

We recently conducted a study to find out if air sacculitis infections in broiler chickens have an effect on carcass weights, percentage of carcasses with fecal contamination, the number of processing errors, and on populations of campylobacter and *E. coli*. We compared air sacculitis-positive flocks with air sacculitis-negative flocks for the factors listed above. In all cases, where differences in the age of the flocks were noted, adjustments were made to the individual carcass weights to account for age differences using the formula (weight for AS carcass + 27.24g x number of days).

Our study showed that air sacculitis-positive carcasses had significantly reduced weight averages in two of five repetitions (Figure 1).

Although not significantly different in three repetitions, the overall average weights were higher for air sacculitis-negative flocks. The net loss averaged over five repetitions was 84g/carcass. For one grow-out house, over a period of one year, the net loss would be approximately 32,379 lbs. as the result of the presence of air sac-

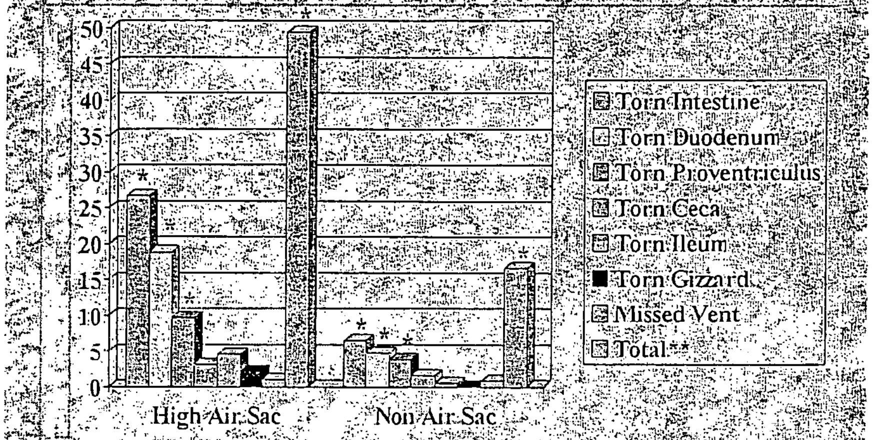
culitis at levels experienced in this study. Moreover, underweight birds are more difficult to process because the evisceration equipment cannot automatically adjust for smaller carcasses when a flock of air sacculitis-positive birds comes into the plant. Overall, air sacculitis had a negative impact on body weight, even though the carcasses selected from air sacculitis flocks in this study were not visibly infected and had already passed inspection. It is possible that the differences in carcass weights would be more pronounced if carcasses that had been removed from the line for visible air sacculitis infections had been weighed and compared to air sacculitis-negative flocks.

In our study, air sacculitis infections significantly increased fecal contamination in four of five repetitions (Figure 2). Thus, it is reasonable to conclude that air sacculitis in flocks of birds may contribute to increases in the risk for human foodborne infection.

We also found that air sacculitis-positive carcasses had a much higher number of processing errors. The combined results (five repetitions averaged) are presented in Figure 3.

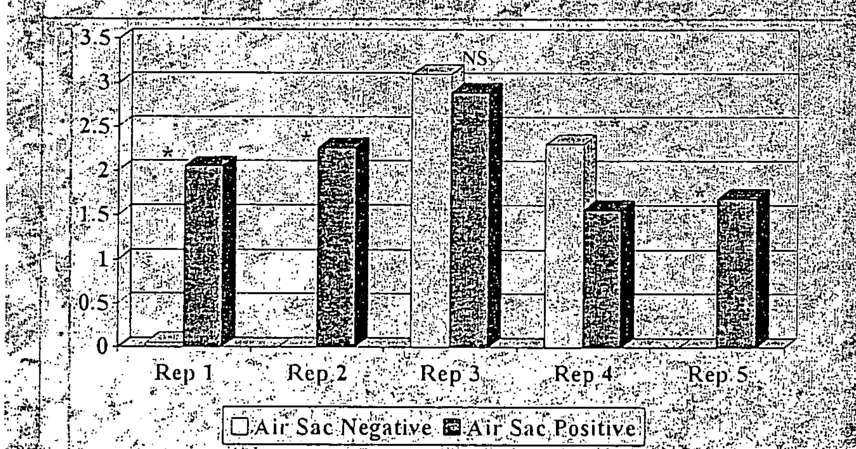
Of particular interest is that the total combined cuts or tears were much higher on air sacculitis-positive carcasses at 49 percent as compared to17 percent for negative carcasses. Low and non-uniform carcass weights may explain why more processing errors occurred in the air sacculitis-positive flocks because the automated equipment in the processing plant is set to receive carcasses of a certain size. Examples of processing errors seen at different locations on the digestive tract are shown in Figures 4-8.

Figure 3. The Effect Of Air Sacculitis On Processing Errors – 5 Replicates



* = Significantly different (P ≤ 0.05) for the same processing parameter between air sac or control
** = The total number of carcasses that had one or more major processing errors

Figure 9. The Effect Of Air Sacculitis On Campylobacter Counts



* = Significantly different (P ≤ 0.05). NS = Not significantly different

Campylobacter Counts

Campylobacter jejuni is now considered worldwide as a leading cause of diarrheal disease and foodborne gastroenteritis (Solomon and Hoover, 1999). It is estimated that *C. jejuni* causes between 1 million to 7 million cases of enteritis per year in the United States, resulting in 100 to 500 deaths (Solomon and Hoover, 1999). Researchers have shown that the intestine of the chicken is the primary reservoir for campylobacter within a flock (Jeffrey *et al.*, 2001). Thus, cut or torn digestive tracts may contribute to campylobacter contamination of the carcass, because if campylobacter is present and the intestines are damaged, the organism may be spread to the carcass.

In our study, campylobacter counts were significantly higher on carcasses from air sacculitis flocks in three of five reps (Figure 9).

In all cases where air sacculitis infections were present, campylobacter was present at levels greater than 1.5 $\log_{10}$

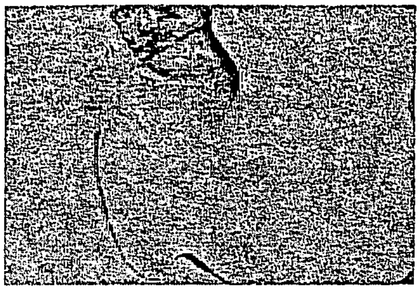


Figure 4. Cut or torn intestine

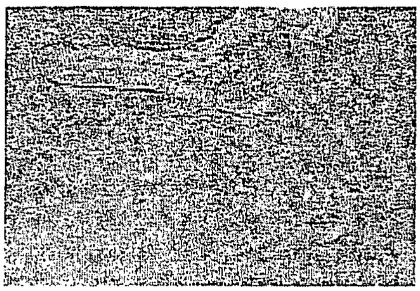


Figure 5. Cut or torn duodenal loop

Figure 6. Cut or torn proventriculus

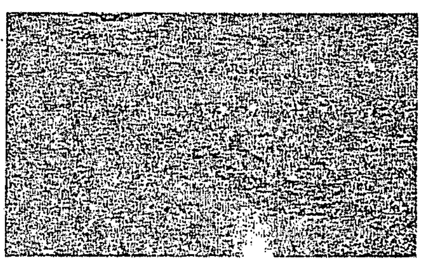


Figure 7. Cut or torn ileal junction and ceca

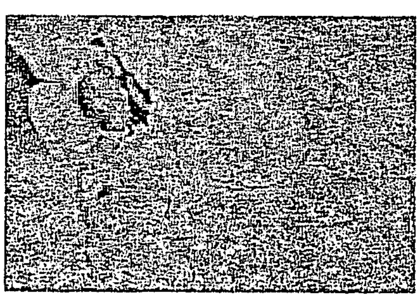


Figure 8. Cut or torn gizzard

CFU/mL. In three of the reps, when air sacculitis was absent, camplyobacter counts were absent or extremely low (< 0.05 $\log_{10}$ CFU/mL). Therefore, there was a relationship between the presence of air sacculitis-positive and campylobacter-positive carcasses.

The data collected in our study suggested that flocks of chickens with air sacculitis infections are more likely to: 1) weigh less than uninfected birds, 2) be contaminated with fecal material during processing, 3) have a processing error or multiple processing errors during venting, opening, and evisceration, and 4) have higher campylobacter counts.

Industrial Data

The results from our study led us to ask the question, if there is a relationship between air sacculitis infections, fecal contamination and indicator and pathogenic bacterial counts in a research study, does this relationship hold up when looking at commercial data from processing plants? To find out, we visited a commercial poultry processor who allowed us to review its records regarding specific processing parameters for 32,300,000 chickens processed over a two-year period. The data were analyzed by the Department of Statistics at the University of Georgia and we looked at the following:

- effects of the presence of air sacculitis infection of birds on fecal contamination of carcasses
- effects of the presence of infectious process on carcasses on fecal contamination of carcasses
- relationship between the number of condemned carcasses and fecal contamination of carcasses
- effect of air sacculitis infection of carcasses on Salmonella prevalence
- air sacculitis infection of carcasses and presence of infectious process on carcasses
- effect of air sacculitis infection of carcasses on carcass weight

The analyses showed that as the percentage of carcasses removed from the line by the USDA inspectors increased, the percentage of carcasses with fecal contamination increased as well. Increasing levels of infectious process also resulted in a significant increase in fecal contamination. The data revealed that when a high number of carcasses are condemned, an increased fecal contamination occurred. A significant finding was that as the number of carcasses removed from the line for active air sacculitis infection increased, the prevalence of salmonella on processed carcasses increased as well. The statistician concluded, "With samples of the size used in this investigation, these differences are quite significant; there is very convincing evidence that air sacculitis increase is associated with increasing probability of salmonella [contamination]." This conclusion strongly supports our research in which we found that the presence of air sacculitis increases campylobacter populations on carcasses and the research obtained from the previous pilot studies. As air sacculitis percentage increased, carcasses with infectious process also increased in a progressive manner. Moreover, carcasses with air sacculitis were significantly lower in weight than carcasses from healthy flocks. The statistician noted, "This analysis displays strong evidence that carcass weight is associated with air sacculitis."

These industrial data show that flocks of chickens that enter the processing plant with air sacculitis infections are more likely to have the following negative parameters associated with processed carcasses arising from these birds: 1) higher fecal contamination, 2) higher salmonella prevalence, 3) higher infectious process, and 4) lower carcass weights.

Likewise, higher infectious process and condemned carcasses (indicating highly diseased flocks) resulted in higher fecal contamination on carcasses.

From the above studies, it becomes apparent that the reduction of air sacculitis in broiler flocks entering the processing plant is a food safety concern. The broiler industry does a good job of vaccinating for the common respiratory viruses that lead to air sacculitis, and there is great emphasis on air quality management, house temperature and feed and water delivery to optimize the broiler immune system. Flock visitations, post-mortem examinations, serology, virus isolation and the principles of epidemiology are employed by veterinarians who specialize in poultry disease control and prevention. However, as with all animal and human populations, disease will occasionally break through these management and vaccination barriers. When this occurs, as with air sacculitis, the last resort becomes antibiotic therapy.

Effective Treatment Vs. Counterproductive Bans

The next question arising from the study was, what is the most effective way to treat air sacculitis infections? A study was conducted at the University of Georgia in which flocks of chickens with active air sacculitis infections were treated with various commonly used antibiotics or no antibiotics (controls). The researchers found that enrofloxacin was the only antibiotic used in the study that was effective for eliminating air sacculitis infections in broiler chickens.

The fact that enrofloxacin is the most effective therapeutic drug for treating air sacculitis raises a number of issues. There is concern that enrofloxacin use in animal agriculture results in the development of antibiotic resistant campylobacter. The European Union was so concerned about the development of resistant forms of bacteria that in 1999 it placed a ban on the use of five growth-promoting antibiotics—avoparcin (a glycopeptide), bacitracin, spiramycin and tylosin (macrolides), and virginiamycin (a streptogramin combination). However, resistance to human analogues of these antibiotics, as well as to fluoroquinolones, has continued to increase in humans since the ban. Also, campylobacter and salmonella infection rates in humans are increasing in Europe (*Eurosurveillance Weekly*, 2002), while they are decreasing in the USA

(CDC, 2002). Some have suggested that the European ban seems to have had a large negative net impact on both animal and human health (Casewell, et al. 2002), although the causes of the continuing rise in illness rates in Europe remain uncertain (*Eurosurveillance Weekly*, 2002).

Currently, the Food and Drug Administration is considering banning the use of enrofloxacin in poultry because of the concern over the development of enrofloxacin-resistant campylobacter in humans. Therefore, an in-depth risk analysis was conducted by Drs. Cox and Popken of Cox Associates, in which they looked at the health risks associated with the use of fluoroquinolones in chickens. They also computed the health benefits for several processing intervention strategies, including banning the use of enrofloxacin in chickens. They concluded that "perhaps surprisingly, the model predicts that a ban on enrofloxacin is expected to increase human health risks of campylobacteriosis by increasing the variance of microbial loads reaching people." The authors found that a person is 9.1 times as likely to get a campylobacter infection if they eat chicken from an air sacculitis-positive flock as opposed to eating chicken from an air sacculitis-negative flock. These data strongly support our research findings, the findings of the pilot study and analyses of industrial processing plant data.

Additionally, another reason that the FDA is considering the ban on enrofloxacin is that a study by Marano (2000) indicated that when people become ill with campylobacter, if the campylobacter are resistant to treatment (antibiotic intervention), these people experience on average an extra two days of illness, resulting in additional health care cost, suffering, and lost work time. However, Cox and Popken found that in the Marano (2000) study, the researchers did not exclude from their analysis, illness associated with foreign travel. When this factor is excluded, the extra days of illness disappear. Therefore, it appears that domestically acquired resistant campylobacter infections pose no greater human health risk than susceptible campylobacter infections. It is also interesting to note that Smith (1999) found 70 percent of resistant campylobacter in Minnesota were associated with foreign travel. Cox and Popken calculated that a nationwide economic loss from increased chicken mortality if enrofloxacin is banned would be $11,692,000 a year. This figure does not include costs of additional air sacculitis condemnations of chickens that survive but do not pass inspection. Nor does it include losses due to smaller average bird weights among airsacculitis-positive flocks.

These studies collectively demonstrate that discontinuing the use of antimicrobials as therapy for air sacculitis (particularly enrofloxacin) may significantly and negatively impact foodborne illness rates in the USA. Moreover, the economic cost and animal welfare issues associated with discontinuing the use of these interventions are significant as well. Finally, the risks associated with the use of these treatments appear to have been miscalculated.

Scott M. Russell, Ph.D., is an associate professor at the Department of Poultry Science, Poultry Science Building, University of Georgia, Athens, GA 30602-2772; Phone (706) 542-1368; E-mail srussell@arches.uga.edu.

References

Bilgili, S.F.; 2001. Poultry meat inspection and grading. *Poultry Meat Processing*, Pages 47-71, A. Sams, ed.

Casewell, M., C. Friis, E.M. Granell, P. McMullin, I. Phillips; 2002. The European ban on growth-promoting antibiotics and its consequences for animal and human health. Report by the European Federation of Animal Health, FEDESA, November, 2002.

CDC, 2002. FoodNet Surveillance Report for 2000 (Final Report). Center for Disease Control and Prevention, FoodNet Surveillance Program.

Cox, L.A., Jr., and D.A. Popken; 2003. Quantifying human health impacts of antimicrobial risk management alternatives for enrofloxacin. Submitted for publication to *Eurosurveillance Weekly*, June 6, 2002, publication.

Jeffrey, J.S., K.H. Tonooka, and J. Lozano; 2001. Prevalence of *Campylobacter spp.* from skin, crop, and intestine of commercial broiler chicken carcasses at processing. *Poultry. Science*, 80: 1390-1392.

Marano, N, D. Vugia, T. Fiorentino, S. Segler, M. Carter, H. Kassenborg, K. Smith, S. Sansky, K. Hollinger, F. Angulo, and the EIP FoodNet Working Group; 2000. "Fluoroquinolone-resistant *Campylobacter* causes longer duration of diarrhea than fluoroquinolone-susceptible *Campylobacter* strains in FoodNet sites". Presented at the International Conference on Emerging Infectious Diseases, July 2000, Atlanta, Ga.

Marrett, J.E., E.J. Robb, and R.K. Frank; 2000. Efficacy of neomycin sulfate water medication on the control of mortality associated with colibacillosis in growing turkeys. *Poultry Science*, 79: 12-17.

Morishita, T.Y., P.P. Aye, B.S. Harr, C.W. Cobb, J.R. Clifford; 1997. Evaluation of an avian-specific probiotic to reduce the colonization and shedding of *Campylobacter jejuni* in broilers. *Avian Dis.*, 41: 850-855.

National Advisory Committee on Microbiological Criteria for Foods, 1997. Generic HACCP application in broiler slaughter and processing. *J. Food Prot.*, 60: 579-604.

Smith, K., J. Besser, C. Hedberg, F. Leano, J. Bender, J. Wicklund, B. Johnson, K. Moore, and M. Osterholm; 1999. Quinolone-Resistant *Campylobacter jejuni* Infections in Minnesota, 1992-1998. *New England Journal Of Medicine*, 340 (20): 1525-1532.

Solomon, E.B., and D.G. Hoover; 1999. *Campylobacter jejuni*: a bacterial paradox. *J. Food Safety*, 19: 121-136.

Turkeys were not alleviated by supplemental dietary vitamin E. *Poultry Science*, 76: 1682-1687.

USDA-FSIS; 1996. Pathogen Reduction: Hazard Analysis and Critical Control Point (HACCP) Systems; Final Rule. *Federal Register*, 61 (144): 38805-38989.

BULLETIN BOARD

Bayer Won't Pull Poultry Antibiotics

Source: BayerWatch.com
Posted: November 1, 2001

Contact: Debra Rosen
202.478.6149/ drosen@mrss.com

WASHINGTON, DC -- Recent threats of bioterrorism have highlighted how important it is to safeguard the effectiveness of America's antibiotics supply. But when the Food and Drug Administration (FDA) recently proposed a ban on the use of certain antibiotics to treat sick chickens and turkeys, Bayer Corporation refused to comply. Instead of removing the antibiotic, Baytril® from the market in response to the FDA's proposal, Bayer has chosen to ignore warnings by scientists and physicians alike that use of their drug in poultry poses a danger to human health.

BayerWatch.com is being launched today to mobilize citizens across the country to tell Bayer to stop playing chicken with public health and to comply with the FDA's proposed ban.

The poultry drug in question, known as Baytril®, is very closely related to a drug used in human medicine, known as Cipro, which is also made by Bayer. Both Baytril® and Cipro are members of a class of antibiotics known as fluoroquinolones. Though Cipro is currently making headlines as a treatment for anthrax, it also plays a key role in treating many other diseases, including severe cases of bacterial food poisoning. FDA proposed the ban after concluding that use of Baytril® contributes to development of flouroquinolone resistance in certain bacteria that cause severe food poisoning.

"Given the importance of this class of antibiotics in human medicine, it just doesn't make sense to be using them in poultry – especially since they are administered via drinking water so that the whole flock is dosed even if only a few birds are sick," said David Wallinga, M.D., of the Institute for Agriculture and Trade Policy. "BayerWatch.com allows citizens across the country to join in the campaign to stop Bayer from putting public health at risk."

Although Bayer has chosen to disregard concerns about antibiotic resistance, health officials are all too aware of this growing public health crisis. Keep Antibiotics Working: The Campaign to End Antibiotic Overuse, was formed to educate the public and policy makers about the need to curb antibiotic resistance. Today, the campaign launches both an activist site, www.BayerWatch.com, focused on Bayer, as well as an informational site, www.KeepAntibioticsWorking.com, which covers a broader range of issues relating to inappropriate use of antibiotics in animal agriculture.

CorpWatch
2288 Fulton St., #103
Berkeley, CA 94704 USA
Tel: 510-849-2423
URL: http://www.corpwatch.org
Email: corpwatch@corpwatch.org

Looking for something on the site? Check out the following:
Home | About | How to Use this Site | Sitemap | Privacy Policy | Feedback

Experiencing technical problems?
Email the web weaver.

US poultry companies halting use of antibiotic

Mail this story to a friend | Printer friendly version

USA: March 4, 2002

CHICAGO - Big poultry producers have flocked quickly this month to rally behind the cause of food safety by banning use of an antibiotic for chickens and turkeys amid rising consumer concerns that it may harm humans.

Perdue Inc., the fifth-biggest U.S. poultry producer, this week became the third top U.S. poultry firm to announce it has stopped using the antibiotic fluoroquinolone, adopting a "zero tolerance" policy towards it.

The move follows similar action taken last week first by top grower Tyson Foods and the second-largest processor, Gold Kist Inc.

All three poultry companies said they each had greatly reduced the antibiotic's use over the past few years and that the new policy was a precaution to allay consumer concerns.

Livestock producers have long used antibiotics to prevent contagious diseases in food animals that are more and more raised in confined spaces.

The concern is that since fluoroquinolone is also used to treat human illnesses, its use in food animals is suspected of causing resistant bacteria that can be transferred to humans, medical sources said.

For example, humans who eat undercooked chicken infected with salmonella can develop serious digestive problems, plus it can kill infants, elderly people, and those with weak immune systems.

"We know there are conflicting studies and a lack of conclusive scientific data on the use of fluoroquinolones," Perdue Farms chairman Jim Perdue said on Wednesday.

"That is why, in the interest of our customers and consumers, we have decided to make an across-the board decision to stop using this antibiotic," Perdue said.

Perdue, which produces 13 million chickens and turkeys a week, said none of its 686 million birds were treated with the drug this past year and less than .01 percent were

4 MAR 2002 ENVIRONMENT NEWS

AUSTRALIA:
Australia denies deal with US risks Kyoto pact

AUSTRALIA:
Australia blasts Japan over whales

AUSTRALIA:
Commonwealth summit security threatens turtles

BELGIUM:
UPDATE - Belgian cabinet approves nuclear phase-out bill

BELGIUM:
Belgian experts see risks without nukes - report

BRAZIL:
Gene-modified food sparks row in Brazil Congress

CANADA:
UPDATE - Greek court annuls permits for TVX Olympias mine

GERMANY:
RWE decides on site for new coal-fired plant

ITALY:
UPDATE - EU, France clash over Mt Blanc tunnel opening

NETHERLANDS:
Dutch set pace on Kyoto treaty ratification

NIGERIA:
Nigeria sets $176 million fine for oil spills

SWITZERLAND:
Battle to ban landmines not won yet - Canada

UK:
UK nuclear clean-up to cost 50 bln stg - minister

UK

treat d with it the year before.

Tyson and Gold Kist said the antibiotic was used on less than 0.2 percent of their chickens.

"WISE MOVE" SAYS MEDICAL COMMUNITY

The medical community praised the moves by Perdue, Tyson Foods, and Gold Kist.

"That comes as great news to us. We think that is a wise move," said Edward Hill, chairman elect of the American Medical Association's board of trustees.

The three companies said they also are reducing the use of all antibiotics in their flocks. They said changes in production practices, selective breeding, and strict bio-security measures have lessened the need for antibiotics.

There are more than 11 million cattle in U.S. feedlots, while the majority of the nation's 52 million market hogs and almost all of its 8 5 billion chickens are raised in crowded pens.

The AMA has been opposed to antibiotic use in livestock production. It praised legislation introduced on Wednesday in the U.S. House of Representatives to gradually phase out the use of some antibiotics fed to animals.

"As you know, antibiotics remain one of the most useful and important medical advances in recent history," the AMA wrote in a letter to Rep. Sherrod Brown, an Ohio Democrat. "Their effectiveness, however, is being compromised by bacterial resistance, arising in part from excessive use of antibiotics in animal agriculture."

Brown was one of three House Democrats who introduced the legislation on Wednesday, which claims such antibiotic use in food animals can create drug-resistant bacteria that can be harmful to humans.

But not everyone opposes antibiotic use in livestock

Dennis Avery, director of the Hudson Institute's Center for Global Food Issues, said antibiotics have been critical in the nation's ability to efficiently increase meat production without increasing land use.

The Center conducts research on agriculture and environmental issues surrounding food and fiber production.

"If we disarm our farmers we are either going to have to accept the kind of food rationing they have in Cuba or we are going to sacrifice a lot of wildlife habitat in order to produce the food that will be demanded," Avery said.

Story by Bob Burgdorfer

REUTERS NEWS SERVICE

FEATURE - Biodiesel fans tout solution to pollution

UK
UK pushes wind, solar power for local communities

UK
Some sheep dippers predisposed to illness - study

UK
Syngenta sees bright GM future even in EU

UK
Amnesty launches appeal for jailed Russian reporter

USA
Senate Republicans fear energy bill may be pulled

USA
UPDATE - Bush defends corporate contacts over energy policy

USA
Odyssey spacecraft sees possible water ice on Mars

USA
NRC says nuke plant's missing fuel rods no threat

USA
Judge raps US delays in energy task force case

USA
Bush names cabinet panel on Oregon water dispute

USA
US regulators propose new fishing restrictions

USA
EU aide sees biotech approvals resuming in fall

USA
China GMO rules - Great Wall or Euro-style caution?

USA
ANALYSIS - US farmers look sold on gene-altered crops

USA
US poultry companies halting use of antibiotic

USA
PSEG gets New York approval for 750-MW gas plant

Antibiotics in Animal Feed Debate Heats Up in the USA

Experts call for limiting antibiotic use
By Steve Mitchell
Medical Correspondent
>From the Science & Technology Desk
Published 5/9/2002 6:21 PM

WASHINGTON, May 9 (UPI) -- A group of antibiotic experts Thursday called for the government and industry to take steps to curtail the use of certain antibiotics in farm animals because the practice could have deadly consequences for humans.

One of the main problems is certain antibiotics are used to promote growth in chickens, cows and other food-producing animals, which can lead to strains of bacteria resistant to the antibiotics, Stuart Levy, president of the Alliance for the Prudent Use of Antibiotics, told United Press International.

Many of these bacteria can then infect people and cause fatal illnesses if antibiotics are no longer effective against them, added Levy, who is also director of the center for adaptation genetics and drug resistance at Tufts University School of Medicine in Medford, Mass.

The increase in bacteria resistant to antibiotics has been a growing problem over the past several years. The main bacteria of concern are salmonella, campylobacter and E. coli. The World Health Organization calculates each year approximately 14,000 Americans die due to drug-resistant infections.

The U.S. government is also concerned about the problem and both the FDA and the Senate are taking steps to curtail antibiotic use in farm animals. The alliance, which held a news conference to discuss the issue and also published a report in the journal Clinical Infectious Diseases, consists of scientists and physicians from around the world who are involved in studying antibiotic resistance.

Their recommendations call for discontinuing the use of antibiotics for growth promotion purposes.

"It's an out-of-date, no longer acceptable practice," Levy said, noting the European Union has banned it.

Although inappropriate use of antibiotics in humans leads to the development of resistance, Levy said, "I could argue that animal use is more pervasive because of the resistant bacteria leaching into the

environment."

Resistant bacteria and the antibiotics are excreted from the animals and leach into soil and water, he said.

Two classes of antibiotics are of major concern -- fluoroquinolones, including the anthrax drug Cipro, and cephalosporins.

Drugs in these classes "may be the last resort for particular diseases" and as such "should be given extra special attention," Levy said. There may be cases where veterinarians or farmers have to use fluoroquinolones or cephalosporins but "they should not be used unless there's no other option," he said.

Levy noted poultry producers Tyson and Purdue have voluntarily cut down on their use of fluoroquinolones and McDonald's and other fast food chains have stopped buying chickens from producers who use the antibiotics.

"We definitely consider this a problem," Linda Tollefson, deputy director of the FDA's Center for Veterinary Medicine, told UPI, noting the agency has proposed a ban on the use of fluoroquinolones in chickens. "Resistance to these antibiotics has developed and it is affecting humans," she said.

However, it may take a year or longer before the ban goes into effect, Tollefson said, because it is currently being challenged by Bayer, which makes the fluoroquinolone Baytril for poultry. Baytril is the same antibiotic used in humans under the name Cipro.

However, legislation to be introduced Thursday by Sens. Edward Kennedy, D-Mass., and Jack Reed, D-R.I., "takes immediate action to implement the decision of FDA to withdraw these drugs from our food supply," the senators said in a release.

The legisation, The Preservation of Antibiotics for Human Treatment Act, will also "protect the health of Americans by phasing out the non-therapeutic use in livestock of medically important antibiotics, unless their manufacturers can show that they pose no danger to the public health." The senators noted the act would "not restrict use of antibiotics to treat sick animals or to treat pets and other animals not used for food."
Other antibiotics the FDA is concerned about include virginiamycin, an antibiotic used to treat a type of bacterial infection called vancomycin-resistant enterococci, which can be fatal in humans, Tollefson said. In animals, virginiamycin is used for growth promotion.

Other growth-promoting antibiotics that can lead to bacterial resisistance include penicillin, tetracycline, streptomycin and erythromycin, all of which are commonly used to treat infections in humans.

Organic Consumers Association
6101 Cliff Estate Rd, Little Marais, MN 55614
E-mail: Staff · Activist or Media Inquiries: 218-226-4164 · Fax: 218-353-7652

Please support our work. Send a tax-deductible donation to the OCA

KEEP ANTIBIOTICS WORKING.com

Take Action News Press Center SEARCH

The Basics
In Depth
For Consumers
The Campaign
Resources
Contact Us
News Bulletin/ Listserve
Sitemap
Home

News

High Bacteria in Poultry Raises Alarm

(Posted: 12-Dec-02)

USA TODAY | Dec. 11, 2002 | Elizabeth Weise

In two studies of chickens sold in food markets nationwide, almost half of those tested were contaminated with bacteria that can pose serious health risks to humans.

And the studies, released today by Consumer Reports and the Sierra Club, found that up to 90% of the bacteria are resistant to common antibiotics.

"Poultry products frequently are contaminated with bacteria that can cause food-borne illness, and often times those bacteria are resistant to the very antibiotics that doctors rely upon to treat them," says the Sierra Club's Ed Hopkins, which jointly commissioned its study with the Institute for Agriculture & Trade Policy. "That's a serious problem, because it means the first drug a doctor gives you may not work," Consumer Reports' R. David Pittle says. You're going to stay sicker longer."

Consumer Reports tested 484 fresh, store-bought chickens from 25 cities and found that 49% were contaminated with either campylobacter or salmonella or both. Of the 155 campylobacter-tainted chickens, 90% were resistant to one or more antibiotics. Of the 58 salmonella-tainted chickens, 34% were resistant to one or more antibiotics.

Of the 200 fresh whole chickens the Sierra Club purchased in Des Moines and Minneapolis, 18% were infected with salmonella, as was 45% of the ground turkey. Almost 6% of the salmonella in the chickens was antibiotic-resistant, as was 62% of the ground turkey. Of 100 of the chickens tested, 95 were infected with campylobacter, 62% of which were resistant to at least one antibiotic.

"We've been reporting similar numbers for several

years now," says Stephen Sundlof, director of the Food and Drug Administration's Center for Veterinary Medicine, which regulates the introduction of antibiotics for animal use but does not regulate use or dosage.

Campylobacteriosis and salmonella can cause diarrhea, fever, abdominal cramps and vomiting. The Centers for Disease Control estimates that there are 30,000 to 40,000 cases each of salmonella and campylobacteriosis each year in the USA, with as many as 100 deaths from campylobacter and 580 from salmonella, says Robert Tauxe, chief of the food-borne and diarrhea diseases branch.

Bacteria in poultry become antibiotic-resistant either through high doses of antibiotics used to treat disease outbreaks or low "sub-therapeutic" doses given to make the poultry grow faster.

The Union of Concerned Scientists estimates 70% of all antibiotics in the USA are fed to pigs, poultry and cattle for reasons other than treating disease.

Richard Lobb of the National Chicken Council says the poultry industry has reduced the use of antibiotics and is now judicious in their use. He says antibiotic resistance also is caused by human overuse and by patients not finishing prescriptions.

However, Tauxe says, "the most commonly identified source of resistant infections is poultry."

The reports call on poultry producers to reduce overall antibiotic use and for better government oversight of antibiotic use in animals.

Return to List

Take Action News Press Center

Field research measures effect of removing GPA from broiler feeds

By WILLIAM A. DUDLEY-CASH

As the result of concern that the wide spread use of growth-promoting antibiotics (GPA) may result in an increase in antibiotic resistance in human medicine, many European countries initiated a ban on the use of GPA in the 1990s. Sweden, for example, formulated a new feed law in 1985 that essentially eliminated the use of all low-level GPA in its animal feeds "cold turkey." The law became effective Jan. 1, 1986.

Reports indicated widespread problems with necrotic enteritis and other chronic enteric problems with poor performance and high mortality. Some reports indicated that the use of therapeutic antibiotics increased to the extent that the total use of antibiotics was higher than before the GPA ban. With improved management, improved housing, lower densities, the use of whole grains and alternative ingredients that modify the intestinal environment, the production problems have become "manageable," though still costly.

The movement to eliminate the use of GPA has been primarily political and consumer driven. There is very little science to support the idea that the use of antibiotics in animal production can be directly associated with increased bacterial resistance in human medicine.

Despite the apparently negative results, consumer pressure has resulted in a spread of the ban on the use of low-level GPA to the extent that as soon as 2005, all GPA may be eliminated from animal feeds in the European Union. Consumer awareness in the U.S. has also encouraged a reduction in the use of GPA to the extent that every broiler company in the U.S. is either producing and marketing some antibiotic-free broilers, field testing the production of antibiotic-free broilers or seriously investigating how to produce antibiotic-free broilers.

What will be the effect on broiler performance of removing GPA from the feed under commercial conditions in the U.S. broiler industry is an important question for which few answers are available.

Engster, Marvil and Stewart-Brown (2002) reported field research designed to evaluate broiler performance in the absence of GPA. "A comprehensive study with close to 7 million growing broilers spanning three years and 158 paired-houses was conducted in two different geographic locations under industry conditions. The purpose of this study was to determine the effect of withdrawing (GPA) from broiler feeds repeatedly on the same farms over a long period in two geographic locations on economically important criteria," the researchers said.

The trial consisted of paired houses on commercial broiler farms. In each comparison, one of the houses was fed a commercial broiler feed including GPA. The other house of the pair was fed the same commercial broiler feed without the inclusion of GPA. The majority of the houses were 40 ft. wide and either 400 or 500 ft. long. Placement density was identical within each pair of houses and ranged from 0.73 to 0.77 sq. ft. per bird. Most houses were tunnel ventilated with dark-out curtains. The equipment within each pair of houses was identical. The number of chicks placed from each of the respective breeder flocks was kept equal for each pair of houses. The majority of birds placed in each facility were of the Perdue breed. The average age at processing was 52 days.

The field trial was conducted in two geographic locations — the Delmarva Peninsula (DP) and eastern North Carolina (NC). At the DP location, a total of 13 farms were used with an average of 9.23 consecutive repetitions of paired houses (a trial house and a control house) on the same farm. The first farm was placed Oct. 8, 1998, and the final farm was settled Sept. 6, 2001.

In NC, there were six farms with an average of 6.17 consecutive repetitions of the paired houses on the same farm. The first farm was placed Oct. 7, 1999, and the last farm was settled Sept. 19, 2001.

In each geographic location, the control houses in each pair were fed the current field coccidiostat program, roxarsone and the GPA program that was in place at that time. The trial houses were fed identical feeds without the GPA program. The GPA program included various combinations of bacitracin methylene disalicylate, zinc bacitracin, bambermycins and virginiamycin in the starter, grower and withdrawal feeds. The coccidiostat

■ *Dr. William A. Dudley-Cash is a poultry and fish nutritionist and has his own consulting firm in Modesto, Cal. To expedite answers to questions concerning this article, please direct inquiries to Feedstuffs, Bottom Line of Nutrition, 12400 Whitewater Dr., Suite 160, Minnetonka, Minn. 55343.*

TABLES

1. The effect of no GPA on bodyweights, feed conversion and color scores[1]

Set of 10 trials[2]	Livability %	Average weight	Feed conversion[3]	Adjusted feed conversion[4]	Color score
DP area					
1. (10/8/98 - 2/17/99)	-0.30	0.01	0.001	0.001	0.04
2. (12/30/98 - 5/14/99)	0.10	0.02	0.012	0.010	-0.04
3. (4/1/99 - 8/17/99)	-0.51	-0.01	0.007	0.007	0.01
4. (7/1/99 - 12/6/99)	-0.10	0.03	0.008	0.003	-0.01
5. (10/21/99 - 2/14/00)	0.10	-0.06	0.011	0.017	-0.01
6. (1/3/00 - 4/21/00)	-0.10	-0.07	0.024	0.030	-0.01
7. (3/14/00 - 7/5/00)	0.20	-0.04	0.038	0.042	-0.06
8. (5/23/00 - 9/13/00)	-0.30	-0.10	0.032	0.041	-0.17
9. (8/1/00 - 12/7/00)	<0.10	-0.06	0.024	0.030	0.00
10. (10/23/00 - 2/21/01)	-0.30	0.07	0.005	-0.002	-0.03
11. (1/4/01 - 5/29/01)	0.30	-0.07	0.021	0.020	-0.05
12. (4/16/01 - 9/6/01)	-0.20	-0.09	0.013	0.023	0.08
Cum. average (120 trials)	-0.10	-0.03	0.016	0.019	-0.02
NC area					
1. (10/7/99 - 6/21/00)	-0.30	-0.10	0.002	0.012	—
2. (7/7/00 - 1/11/01)	0.00	-0.06	0.017	0.023	—
3. (11/21/00 - 7/16/01)	-0.20	0.00	0.006	0.008	—
4. (5/21/01 - 9/18/01)[5]	-0.10	0.01	0.022	0.021	—
Cum. average (37 trials)	-0.14	-0.04	0.012	0.016	—

[1]The results are reported as the difference between the control house and the trial house results (trial without GPA minus the control)
[2]Placement date of the first flock in the group - movement date of the last flock in the group
[3]Feed conversion = (lb. feed/lb. bodyweight gain)
[4]Bodyweight of 0.01 lb. = 0.01 feed conversion.
[5]Set of seven trials

2. The effect of no GPA on percent farm and total condemnations[1]

Set of 10 trials[2]	Air sacculitis	Septicemia	Leukosis	Inflamm. process	Tumors	Farm condem. total	Total condemnations
DP area							
1. (10/8/98 - 2/17/99)	-0.07	0.07	-0.16	-0.04	-0.06	-0.42	-0.42
2. (12/30/98 - 5/14/99)	-0.06	-0.03	-0.03	0.00	-0.03	-0.15	-0.14
3. (4/1/99 - 8/17/99)	0.03	0.08	-0.06	0.05	-0.05	0.03	0.15
4. (7/1/99 - 12/6/99)	0.00	-0.01	0.00	0.03	0.00	0.00	0.04
5. (10/21/99 - 2/14/00)	-0.02	0.03	0.01	0.03	0.00	0.05	0.13
6. (1/3/00 - 4/21/00)	0.35	-0.03	0.10	0.00	-0.02	0.03	0.01
7. (3/14/00 - 7/5/00)	0.00	0.23	0.02	0.03	0.03	0.29	0.31
8. (5/23/00 - 9/13/00)	0.01	-0.10	-0.08	0.00	-0.03	-0.02	-0.15
9. (8/1/00 - 12/7/00)	0.01	0.23	0.02	0.01	0.04	0.33	0.44
10. (10/23/00 - 2/21/01)	0.00	0.12	0.02	0.01	0.01	0.01	0.15
11. (1/4/01 - 5/29/01)	0.00	0.06	0.02	0.00	0.01	0.10	0.08
12. (4/16/01 - 9/6/01)	0.00	0.00	0.01	0.00	0.01	0.00	-0.20
Cum. average (120 trials)	-0.01	0.04	0.01	0.00	-0.01	0.01	0.03
NC area							
1. (10/7/99 - 6/21/00)[3]	0.03	-0.03	0.00	-0.10	0.02	-0.08	-0.07
2. (7/7/00 - 1/11/01)[3]	0.01	-0.05	0.00	0.01	0.00	-0.03	-0.13
3. (11/21/00 - 7/16/01)[3]	0.00	-0.04	0.00	0.06	-0.14	-0.11	-0.17
4. (5/21/01 - 9/18/01)[3]	0.00	-0.06	0.00	0.00	0.02	-0.06	-0.11
Cum. average (31 trials)	0.01	-0.03	0.00	0.00	-0.03	-0.08	-0.12

[1]The results are reported as the difference between the control house and the trial house results (trial [without GPA] minus the control [with GPA])
[2]Placement date of the first flock in the group - movement date of the last flock in the group
[3]Set 1 contained six trials, set 2 contained 10 trials, set 3 contained nine trials and set 4 contained six trials

10

roxarsone and GPA programs were rotated approximately every four months during the course of this study. All diets were corn-soy based and were nutritionally balanced for the Perdue breed.

Results

Table 1 shows the results for livability, average weight at processing, feed conversion, adjusted feed conversion and color score. The results are reported as the average differential (trial house without GPA minus control house with GPA) for 10-paired house comparisons. At the DP location, there were a total of 12 groups of 10-paired house comparisons (120 paired house comparisons).

In the case of livability, a negative number would show that the control houses had a higher livability than the trial houses. For average weight, a negative number shows that control houses weighed more than the trial houses. For feed conversion and adjusted feed conversion, a positive number shows that the trial houses had a higher feed efficiency or adjusted feed conversion than the control houses. In the case of color score, a negative number indicates the control houses had a higher score than the trial houses.

The results in Table 1 for the DP area shows an average negative impact of 0.1% on livability when GPA was removed from the feed. The largest negative impact for livability was 0.51% (set 3) while set 11 showed a positive response of 0.3%, the largest positive response in livability to the removal of GPA.

The average difference in bodyweight was a negative 0.03 lb. There did not appear to be any effect on bodyweight for about the first year (through the first four sets of data). Beginning with the fifth set of data, there was a fairly consistent negative effect from the removal of GPA.

Feed conversion also was not aversely affected much more than about 0.01 lb. feed per pound of gain until after the first year. From the sixth through the ninth data sets, there was a consistent increase in feed conversion observed. Beginning with the 10th data set, the increase in feed conversion was much less. The weight-adjusted feed conversion followed a similar pattern as the unadjusted feed conversion.

The authors reported that color scores, on a scale of 1 to 5, were amazingly uniform throughout the entire study in the DP area. The average differential in color score was only 0.02 between the trial and control groups.

The average results in the NC region were similar to the results observed for the DP region. Livability was decreased an average of 0.14%, average weight was decreased an average of 0.04 lb., feed conversion was increased an average of 0.012 and adjusted feed conversion was increased an average of 0.016.

The authors pointed out that the decrease in weight gain occurred immediately in the first two groups of 10 comparisons in the NC region, while this was not the case in the DP region.

An important observation by the authors was that the lack of any substantial difference in mortality in either geographic location was coupled with no field observations or veterinary reports of any outbreaks of dermatitis, necrotic enteritis or dysbacteriosis. These problems have repeatedly been reported in the U.K. and EU following the removal of GPA.

Table 2 shows the impact of removing GPA from the diet on farm and total condemnations in the processing plant. Over the course of the entire study, the data show there was little, if any, difference in farm condemnations with or without GPA. The data from the NC area also show little, if any, effect of GPA removal on farm and total condemnation. In the NC region, there was actually a small but consistent indication of a positive response.

Regarding condemnation, this columnist would like to point out that in the DP region, the numbers 7 and 9 sets of trials appeared to be quite different from the other sets of data in regard to condemnation. If these two sets of data were removed, the average for septicemia condemnation and total condemnations would all be negative, indicating a slight advantage in this region for the removal of GPA from the feed.

A comparison of bird uniformity was made in one pair of houses in the DP region. A total of 250 males and 250 females were individually weighed in the trial and control houses. The results suggested there may be a decrease in uniformity as a result of removing GPA from the feed.

A total of six individual farms in the DP region were evaluated for the effect of changing to new litter in the house. The three consecutive flocks prior to changing to new litter were compared with the three consecutive flocks following the change to new litter. Livability, weight gain and weight-adjusted feed conversion were measured. There appeared to be an improvement in livability in the first and second cycles following the change to new litter, but by the third cycle, this improvement had completely disappeared.

The effect on broiler market weight was quite different. The authors stated that the data showed no improvement in weight gain for the trial (no GPA) treatment as the result of new litter. If anything, the data suggest that the weight gain difference between no GPA and plus GPA became greater, especially in the second and third cycles after the birds were put on new litter. The results showed there was minimal improvement in weight-adjusted feed conversion in the first cycle after changing the litter.

The differential in adjusted feed conversion, between the trial and control houses, progressively favored the control houses with the second and third cycles. Overall, the data indicated that any effect of changing litter in an attempt to improve performance and livability when GPA are removed from the feed was, at best, a short-term gain.

Bottom Line/ p. 12

...S. free of BSE."
USDA tested
...sing a targeted
...lesigned to test
...als, including
...ls that are non-
...), animals that
...imals and ani-
...f neurological
2001, USDA

...ficantly higher
...the Office In-
...ies (OIE), the
...ation for ani-
...rnational stan-
...y like the U.S.
...only 433 head
...said it is now
...ount.
...illance, OIE
...risk analysis
..., an education
...and compul-
...ments in order
...that it is BSE
...ese criteria in

case. The fol[illegible]ng is an update on those actions[illegible]

• **Peer review of Harvard risk assessment to ensure scientific integrity:** Following publishing of the Harvard risk assessment, USDA identified several independent scientists to conduct independent analysis on the report. The group of scientists expects to complete their work by June 2003.

• **Double the number of BSE tests:** As stated, USDA has exceeded that goal by conducting nearly 20,000 tests in fiscal 2002, more than tripling the number of tests over the previous year.

• **Publish a policy options paper outlining additional regulatory actions:** In January 2002, the Food Safety & Inspection Service (FSIS) published a current thinking paper on BSE policy measures to consider public comments on future regulatory and policy recommendations. This included actions regarding advanced meat recovery (AMR) systems and prohibiting the use of vertebral column from certain categories of cattle.

In June 2002, FSIS announced proposals. FSIS will seek these additional comments on a recently completed s[illegible] regarding AMR systems using beef vertebral columns as source material. The proposed rule will clarify that vertebral column should not be used as a source material unless the establishment has effective process control measures in place to ensure that central nervous system tissue is not present in meat derived from AMR systems. A final rule is expected on AMR by December 2003.

• **Rule to prohibit use of certain stunning devises:** FSIS is working to complete a direct final rule by March 2003 prohibiting the use of air-injection stunning devices used to immobilize cattle during slaughter. In this rulemaking, FSIS will address the risk posed by stunning devices that may inadvertently force visible pieces of brain and spinal ...

2003, the Animal & Plant Health Inspection Service also plans to issue an ANPR to consider additional regulatory options for the disposal of dead stock on farms and ranches. Such cattle are considered an important potential pathway for the spread of BSE in the animal feed chain.

Since 1989, the U.S. government has taken a series of preventive actions to protect against this animal disease. This includes USDA prohibitions on the import of live ruminants, such as cattle, sheep, goats and most ruminant products from countries that have or are considered to be at risk for having BSE. In 1997, FDA prohibited the use of most mammalian protein in the manufacture of animal feed intended for cows and other ruminants to stop the way the disease is thought to spread. ■

Bottom Line: GPA tested/ *From p. 11*

Discussion

The results of this research show that there is a small but relatively consistent reduction in broiler performance when GPA is removed from the feed. While the differences small, they are clearly economically important. Small differences in performance are frequently the difference between profit and loss in the broiler industry.

Surprisingly, the health status of the flocks did not appear to be affected by the removal of GPA from the feed. In the course of this three-year study, there were no reports of field outbreaks of dermatitis, necrotic enteritis or dysbacteriosis. This was consistent with the finding of no significant differences in septicemia or inflammatory process in the processing plant. Total farm condemnations were not affected by the removal of GPA.

This might almost be categorized as an unexpected result. There have been many reports from the EU of necrotic enteritis and other enteric problems associated with the removal of GPA from the feed.

The authors should be commended for the scale of their research and the value of their report. Field research, even under the best of conditions, is a major challenge. Organizing several hundred people to get the correct feed in the correct feed tank, the correct birds loaded on the right truck and finding those birds in a commercial processing plant is an accomplishment.

Every broiler company is growing some birds without GPA in the feed or seriously contemplating the removal of GPA from their feed. This is the kind of field experience that will be very helpful in making that decision.

This research does not address several issues. The coccidiostat program and the use of roxarsone were not described in any detail in the published paper. "Ionophore was in the feed most of the time but not all of the time," according to a personal communication. The use of an ionophore coccidiostat has been reported to be the most effective ingredient for suppressing necrotic enteritis and maintaining health status when GPA is removed from the feed. How would the broilers perform if ionophore coccidiostats were completely eliminated from the feed when the GPA is removed? Ionophore coccidiostats will also be banned from poultry feed in the EU as early as 2005.

Roxarsone is also effective in promoting better broiler health. Roxarsone is not used in broiler feed in the EU. What would be the effect of eliminating the roxarsone when GPA is removed from the feed? Some breeds of birds have a stronger immune system and are just plain "tougher." This research was conducted with the Perdue breed. How would other breeds perform under the same conditions?

My guess is that the growers and broiler houses used in this research were average or better than average in their management levels. In a field research program, there is a strong incentive to choose the better people just because they are more likely to follow directions correctly. Arguably, these research houses received special attention. A little special attention always improves performance. How will the birds perform for average or below average growers when GPA is removed from the feed? More than half of our growers and facilities are average or below.

The authors stressed that "It is important not to rely on limited data from a single location over a short period when making a decision of whether or not to remove GPA from the diets of broilers."

The Bottom Line

The removal of GPA from the feed resulted in small but relatively consistent reductions in broiler performance. There appeared to be little or no effect on bird health. Most importantly, there were no disasters.

REFERENCE

Engster, H.M., D. Marvil and B. Stewart-Brown. 2002. The effect of withdrawing growth promoting antibiotics from broiler chickens: A long-term commercial industry study. J. Appl. Poult. Res. 11:431-436. ■

KEEP ANTIBIOTICS WORKING.com

Take Action News Press Center SEARCH

The Basics
In Depth
Resources
About the Campaign
Contact Us
Subscribe to News Bulletin
Join ListServ
Home

News

Strep And Overuse Of Antibiotics

(Posted: 17-Mar-03)

Tampa Tribune | March 13, 2003 | Editorial

Researchers at the Harvard School of Public Health predict that by the summer of 2004, 40 percent of strep infections in the United States will be resistant to penicillin and erythromycin, the leading antibiotics.

The discovery emphasizes the urgent need to curtail the promiscuous use of antibiotics, which are often prescribed when not needed and are commonly used in livestock operations.

Such use, as the latest research indicates, can have dire consequences.

Antibiotics are truly wonder drugs that have saved millions of lives, but their effectiveness is reduced when they are overused and bacteria develop an immunity to them.

This is unlikely to happen if the drugs are used only when needed. But they are often used inappropriately. Antibiotics, for instance, have no effect on viruses, the cause of most colds. Yet people often want - and doctors often prescribe - antibiotics as soon as they come down with a sore throat and the sniffles.

Health officials estimate perhaps as much as half of the 100 million antibiotic prescriptions written in doctors' offices each year are unnecessary.

The rapid development of strep resistance to both of the leading antibiotics is truly frightening, meaning a virulent infection that now can be readily treated will become increasingly more difficult to knock out. Lives will be jeopardized.

While the Harvard researchers' findings are

alarming, they should not surprise. Physicians have long warned of the overuse of antibiotics.

Last year an article by a Finnish doctor in the New England Journal of Medicine reported that the prevalence of strep that could not be treated with a certain form of antibiotic began increasing in 1990. When regulations limited the drug's use, the resistance problem diminished.

But it's not just medical use that accounts for people's exposure to antibiotics. The drugs are commonly used in livestock operations to promote growth in animals raised for human consumption

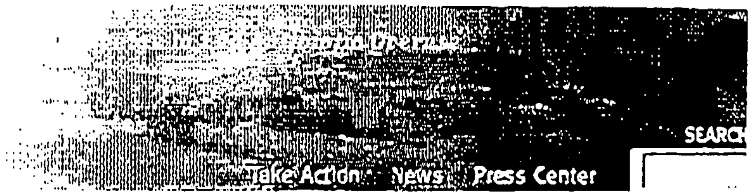
These antibiotics too often end up in people. A study last year found a high rate of antibiotic-resistant salmonella in ground meat. Another study found antibiotic-resistant bacteria in slaughtered chickens and pigs can remain in the intestinal tract of humans for two weeks or more.

Researchers have found some antibiotics with promising human uses have been compromised by their use for livestock.

The situation cries for reform, yet the agriculture industry continues to fight better controls.

The plain fact is that the reckless use of antibiotics is breeding dangerously tough strains of bacteria. We hope it does not take an epidemic of deadly, super-tough strep to make the nation's leaders recognize the need for tougher standards for antibiotic use.

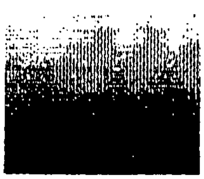
KEEP ANTIBIOTICS WORKING



The Basics
In Depth
Resources

About the Campaign
Contact Us

Subscribe to News Bulletin
Join ListServ
Home



News

University of Buffalo Chemist Traces the Environmental Fate of Antibiotics Used with Livestock from Barnyards to Crop Fields

(Posted: 25-Mar-03)

Release date: Monday, March 3, 2003 Contact: Ellen Goldbaum, goldbaum@buffalo.edu Phone: 716-645-5000 ext 1415 Fax: 716-645-3765

BUFFALO, N.Y. -- Besides producing the raw material that ends up as the roast beef or ham on your dinner table, livestock farms also are big producers of manure. Farmers get rid of manure in an environmentally responsible way, by turning it into fertilizer for their fields or those of other farmers.

But deep in those piles of dung lie not just beneficial, organic matter, but the residues of antibiotics used to promote growth in livestock and to treat their diseases.

How much of these antibiotics ends up in the environment, and thus could potentially alter microbial ecosystems in humans, animals and the environment is the focus of research being conducted by Diana Aga, Ph.D., assistant professor of chemistry in the University at Buffalo College of Arts and Sciences.

"A lot of research is done to study how antibiotics used in human medicine result in the development of resistance in microorganisms," explained Aga, "but how about microbial resistance due to exposure to antibiotics in the environment?"

She explained that people may be infected by resistant pathogens in the environment through direct contact or by indirect means, such as through the food supply.

Aga is one of a handful of scientists in the world looking at the question from a unique vantage point, taking into consideration the

complete journey made by animal antibiotics and their metabolites from the barnyard to the crop field and, possibly, to supplies of drinking water.

While other researchers, particularly those at government agencies such as the U.S. Geological Survey, examine the ultimate destination of antibiotics, such as levels found in rivers and groundwater, those studies do not distinguish between antibiotics excreted by animals or humans, Aga explained.

"Direct evidence that links antibiotic use in animal production and resistance in bacteria that infect humans is lacking," said Aga. "We are only now beginning to do the studies that will be able to address that issue."

She noted that government agencies, such as the USDA and the FDA, are being pressured by environmentalists to ban the use of antibiotics as growth promoters in animals.

"But there are a lot of economic issues to consider before taking that step," explained Aga, who noted that in Switzerland, Denmark and Sweden such bans of antibiotics as growth promoters are already in place.

When drugs are administered to animals, whether it's to treat diseases or for growth promotion, as much as 50 per cent or more is not metabolized and is excreted by the animal intact, Aga explained.

"So when manure is used to fertilize fields, you're now exposing the microorganisms in the soil to low levels of these drugs, creating the perfect conditions for selectively proliferating resistant bacteria," she said.

"In our studies of swine and cattle manure, we found between 5 ppb (parts per billion) and 20,000 ppb of tetracycline, which is really high," said Aga.

Tetracycline, which is prescribed to combat a broad range of bacterial infections in humans, also is used as a growth promoter in pigs.

Aga noted that levels of antibiotics in animals vary depending on the stage of life.

"For example, when a pig is almost ready for slaughter, the use of antibiotics is curtailed to ensure that the meat is not contaminated with antibiotics," she said.

Aga is framing her findings in terms of how farmers can minimize the potential for the

development of resistant bugs in fertilized soil

Her findings so far confirm other results that have identified loamy soils as those that can be safely applied with fertilizer.

"The sandier soils are not good candidates for fertilizing with manure that may be contaminated with antibiotics because the antibiotics could leach easily before they can break down sufficiently

"But that's not the case with loamier soils," she said, "In fact, after two weeks, we have seen as much as 50 per cent degradation."

According to Aga, if antibiotics degrade quickly in the field, they will not likely pose a problem. Like pesticides and other environmental pollutants, degradation is slowed down in colder, less sunny environments, she added.

"Our work is focused on understanding the fate, transport and ecotoxicological impacts of antibiotic residues in the environment," she said. "We hope to offer fundamental knowledge that could be used as a basis for developing management practices and policies that could prevent contamination of soil and aquatic systems."

"Manure is a very good source of organic fertilizer. We don't want to overreact," said Aga, whose parents run a small poultry farm in the Philippines.

Aga is organizing an international symposium, "Ecotoxicity and Environmental Chemistry of Antibiotics," for the annual meeting of the Society of Environmental Toxicology and Chemistry to be held in November in Austin, Texas. The symposium will bring together scientists from different countries to share results in the field and build collaborations.

KEEP ANTIBIOTICS WORKING.com

News

Improper Antibiotic Use Endangers Us All

(Posted: 25-Mar-03)

London Free Press | March 17, 2003 | Dr. Gavin Hamilton |

A recent CP article in The Free Press, Canadians warned about antibiotic abuse (Feb. 26), brings up the important issue of the menace of antibiotic resistance in disease-causing bacteria.

Antibiotic resistant strains of bacteria have been surfacing since the 1950s, when hospitals began to experience staphylococcal infections that failed to respond to penicillin. This was the result of using therapeutic doses that were not high enough and using antibiotics when they weren't really needed. Even then, doctors were being cautioned about he improper use of antibiotics.

As new antibiotics were developed, the medical profession became somewhat complacent, using antibiotics unnecessarily, often because of pressure from patients or even nursery schools when children became sick. Using antibiotics for viral infections such as influenza, or the common cold, or using preoperative antibiotics instead of adhering to strict sterilie procedures in the operating room, is just a small part of the problem.

In keeping with Darwin's survival of the fittest, we find that the unnecessary use of antibiotics kills off many bacteria, but those that survive are not only antibiotic-resistant, but some tend to be far more dangerous to humans.

A good example of this is the E. coli 0157:H7 that caused bloody diarrhoea, severe kidney damage and deaths in Walkerton. These antibiotic resistant E. coli came from a regional livestock operation.

While the medical community is striving to

achieve rational selective use of antibiotics, large livestock operations routinely use an antibiotic-feed mix, administering subtherapeutic doses of antibiotics to all of their healthy animals, just to achieve a marginal increase in meat production, while making large profits for the makers of the antibiotics.

In 1998, the World Health Organization noted that more antibiotics were being used in feed for healthy animals than were used to treat human disease, a situation that defies the most fundamental principles of public health.

Factory livestock farms produce very large volumes of manure, often on very small acreages (particularly true of factory pig farms). Such pig farms produce volumes of animal sewage equal to a moderate sized town. Because of routine antibiotic use in feed, this sewage is laced, not only with antibiotics, but with antibiotic resistant bacteria. These potentially lethal bacteria can survive for long periods in the manure pile and in water tables that they contaminate with great ease. It is the contamination of water tables that poses the greatest risk.

There are two frightening recent discoveries. One is the ability of vegetable root systems to ingest these lethal organisms into the internal structure of the edible plants. The second is the ability of bacteria sharing the same environment to transfer their antibiotic resistance to unrelated organisms by transferring antibacterial resistance genes from one to the other. This means that, in the manure pile or in water systems (streams, water tables, lakes and ponds), antibiotic resistance can be transferred by E. coli to unrelated Salmonella, or vice versa.

In 1997, the World Health Organization (WHO) recommended antibiotics be prohibited for use in healthy animals for growth promotion in cattle, sheep, pigs and poultry. The WHO condemned using antibiotics as a substitute for good animal hygiene. They noted European farmers who stopped relying on antibiotics as growth promoters experienced no economic repercussions.

While physicians are successfully striving to curb unnecessary antibiotic use, why are North American factory farms allowed to produce potentially lethal strains of resistant bacteria (which they release into our water tables and environment) by using more antibiotics on healthy animals than are used to treat disease in our patients? Can the pharmaceutical industry justify putting everyone at risk to maintain large profits from this flagrant abuse of antibiotics? Is behind-the-scenes lobbying by a powerful industry putting us, our children and our future at grave risk by delaying, or blocking laws that

would eliminate antibiotic use in healthy animals?

NOTES: Vox Pop provides readers with an opportunity to comment on topical issues. Dr. Gavin Hamilton is a London physician.

JAC

OXFORD
Journals *online*

Advance Access published July 1, 2003, 10.1093/jac/dkg313
Journal of Antimicrobial Chemotherapy (2003) 52, 159-161

- Full Text of this Article
- Reprint (PDF) Version of this Article
- Email this article to a friend
- Similar articles found in:
  J. Antimicrob. Chemother. Online
  PubMed
- PubMed Citation
- Search PubMed for articles by:
  Casewell, M. || Phillips, I.
- Alert me when:
  new articles cite this article
- Download to Citation Manager

Review

The European ban on growth-promoting antibiotics and emerging consequences for human and animal health

Mark Casewell[1,*], Christian Friis[2], Enric Marco[3], Paul McMullin[4] and Ian Phillips[1]

[1] University of London, London; [4] Poultry Health Services Ltd, Thirsk, North Yorkshire, UK; [2] Royal Veterinary and Agricultural University, Copenhagen, Denmark; [3] B & M Consulting, Barcelona, Spain

Received 19 December 2002; returned 20 March 2003; revised 27 April 2003; accepted 28 April 2003

Following the ban of all food animal growth-promoting antibiotics by Sweden in 1986, the European Union banned avoparcin in 1997 and bacitracin, spiramycin, tylosin and virginiamycin in 1999. Three years later, the only attributable effect in humans has been a diminution in acquired resistance in enterococci isolated from human faecal carriers. There has been an increase in human infection from vancomycin-resistant enterococci in Europe, probably related to the increased in usage of vancomycin for the treatment of methicillin-resistant staphylococci. The ban of growth promoters has, however, revealed that these agents had important prophylactic activity and their withdrawal is now associated with a deterioration in animal health, including increased diarrhoea, weight loss and mortality due to *Escherichia coli* and *Lawsonia intracellularis* in early post-weaning pigs, and clostridial necrotic enteritis in broilers. A directly attributable effect of these infections is the increase in usage of therapeutic antibiotics in food animals, including that of tetracycline, aminoglycosides, trimethoprim/sulphonamide, macrolides and lincosamides, all of which are of direct importance in human medicine. The theoretical and political benefit of the widespread ban of growth promoters needs to be more carefully weighed against the increasingly apparent adverse consequences.

Keywords: growth promoters, Europe, antibiotic use

* Correspondence address. Department of Infectious Diseases, Guy's, King's & St Thomas's School of Medicine (King's College Hospital Campus), Bessemer Road, London SE5 9RS, UK. Fax: +44-20-7346-3404; E-mail: casewell@netcomuk.co.uk

14

Reprinted with the permission of Reuters.

USA: STUDY FINDS TAINTED, DRUG RESISTANT MEATS COMMON.
October 18, 2001
By Gene Emery

Harmful bacteria in meat and poultry are becoming more resistant to antibiotics due to the long-controversial practice of feeding the drugs to cattle and other food animals, according to research published in Thursday's New England Journal of Medicine.

The practice of giving healthy livestock antibiotics to promote growth and profits makes salmonella and similar organisms that sometimes can cause severe diseases immune to the drugs and should be scrapped, according to an accompanying editorial. The new research, along with previous studies "represent the proverbial smoking gun" that demonstrates why it is time to stop feeding antibiotics to livestock, said Dr. Sherwood Gorbach in the editorial.

Gorbach, of the Tufts University School of Medicine in Boston, said antibiotics should only be given to individual animals that have been examined by a veterinarian, and even those animals should not be allowed to receive antibiotics that are important for curing human disease. In addition, he said, the practice of giving antibiotics to animals to promote growth should be banned. Researchers have been trying to raise the alarm for years about the widespread practice of feeding antibiotics to food animals.

The Union of Concerned Scientists, a science-based advocacy group opposed to the use of antibiotics in livestock, estimated earlier this year that while 3 million pounds (1.3 million kg) of antibiotics are given to humans each year, 26.6 million pounds (12.1 million kg) are given to animals. About 24.6 million pounds (11.2 million kg) of that goes to animals that are not sick.

Doctors may play a role in breeding antibiotic resistance because they overuse the drugs in humans, but the widespread use of antibiotics in animals contributes to the problem, Gorbach said. Proponents of animal antibiotic use contend the drugs make food production more efficient and profitable, Gorbach said. However, he said, "there are alternatives, as shown in Europe after the use of these drugs was abandoned. The economic losses could be minimized and even neutralized by improvements in animal husbandry, the quality of feed, and hygiene."

Nearly 1.4 million cases of salmonella poisoning occur in the United States each year from eating contaminated beef, pork, poultry, eggs and milk. The risk is highest among the elderly and people whose immune systems are not working properly. In the latest study, investigators from the Food and Drug Administration found that 20 percent of the 200 samples of ground chicken, beef, turkey, and pork purchased at three Washington D.C.-area supermarkets contained salmonella, which causes food poisoning.

In addition, 84 percent of those salmonella bacteria were resistant to at least one type of antibiotic; 53 percent were resistant to three. Another study in the Journal tested chicken products in four states and found 17 percent harbored drug-resistant bacteria.

15

Judicious Use of Antimicrobials for

Poultry Producers

Principles of Judicious Therapeutic Use of Antimicrobials (Antibiotics)

Their Application for Producers in the Poultry Industry

Introduction

The principles of judicious therapeutic antimicrobial use were developed and approved by the American Veterinary Medical Association to serve as a guide for veterinarians to use therapeutic antimicrobials (antibiotics) in order to maximize therapeutic efficacy while minimizing the development of resistance. The AVMA defines therapeutic as use for the treatment, control, and prevention of bacterial disease.

Antibiotic resistance is a global problem that affects both humans and animals. The development of resistance is a consequence of the use of antimicrobials. Concerns about the use of antibiotics in food producing animals involve food safety issues because meat products from animals have been identified as transfer vehicles for food borne illness in humans. It is imperative that everyone involved in food animal production, veterinarians and producers, as well all human health care providers work together in minimizing the development of antibiotic resistance.

This document is written for use by producers of poultry. All producers involved in poultry production should familiarize themselves with the principles of judicious therapeutic use of antibiotics to insure that a cooperative effort is established by the producer and veterinarian in the control and antibiotic treatment of bacterial diseases of poultry.

The following principles of judicious therapeutic antibiotic use

should be considered by producers to maximize the benefits of therapeutic antibiotic use while minimizing the development of resistance.

Judicious Use Principles for Poultry Producers

Preventive strategies, such as appropriate husbandry and hygiene, routine health monitoring, and immunization, should be emphasized.

The foundation of the success in the poultry industry is through effective management practices that prevent disease. The foundation of biosecurity (preventative disease management) starts with the producer. Farms utilizing all-in-all-out production minimize the presence of multiple ages of flocks on farms to help in disease prevention. Biosecurity programs on poultry farms should be in place to help prevent the introduction of diseases. The appropriate use of coveralls, boots and head coverings prevents the introduction and spread of disease within and between farms. Producers should also work with veterinarians and health specialists to establish sound disease prevention programs based on vaccination strategies to reduce disease outbreaks in poultry. The poultry industry is the leader in novel procedures for vaccination of large numbers of poultry. Breeder and meat production flocks should be monitored for protective response to vaccinations. Serological monitoring of disease exposure forms the basis of strategic vaccination programs. An effective way of minimizing antibiotic resistance is to avoid antibiotic use through the prevention of disease exposure and/or vaccination to achieve protection against disease outbreaks.

Other therapeutic options should be considered prior to

antibiotic therapy.

Poultry producers should approach the treatment of diseases with antibiotics very cautiously. Because of the cost of disease treatment with antibiotics, therapeutic antibiotic intervention should be used only as one tool to treat active disease. Management adjustments should be made when disease outbreaks occur by reacting to environmental temperature, ventilation, and litter moisture to minimize the impact of any disease condition in flocks. Supportive therapy with vitamins and electrolytes may be utilized in some cases of disease outbreaks to help avoid the use of antibiotics. All management and non-antibiotic intervention strategies should be explored and a veterinarian or health specialist consulted prior to the use of antibiotics.

Judicious use of antibiotics, when under the direction of a veterinarian, should meet all requirements of a valid veterinarian-client-patient relationship.

A valid veterinarian-client-patient relationship (VCPR) must be established at any time prescription antibiotics are used or any antibiotic is used **not** in accordance to labeled directions. It is against federal law to use prescription antibiotics or antibiotics in an extra-label manner without an established valid VCPR. A valid VCPR means that certain conditions are met prior to the initiation of treatment:

1) **A veterinarian must be involved**. The veterinarian assumes responsibilities in making a clinical judgment and/or diagnosis in the flock. He/she is knowledgeable about the health status of the flock. The producer

agrees to follow the directions of veterinarian;

2) The veterinarian has sufficient knowledge of the flock, has recently seen the flock, and is knowledgeable with regards to the management of the flock;

3) The veterinarian is available for consultation and follow-up evaluation of the antibiotic treatment.

The VCPR should be established and followed in all flocks prior to antibiotic therapy. Poultry producers in integrated poultry companies should consult the company veterinarian prior to the initiation of any antibiotic treatment. Veterinarians should closely monitor antibiotic use in their poultry flocks. They maintain close contact with service technicians and managers related to the use of antibiotics. Antibiotics should always be used under the direction and knowledge of the company veterinarian or veterinary consultant.

Prescription, Veterinary Feed Directive, and extra-label use of antibiotics must meet all the requirements of a valid veterinarian-client-patient relationship.

At the present time, no feed additives are approved for prescription or by veterinary feed directive in poultry. If these products are approved in the future, strict compliance with regulations must be followed with the same policies set for other antibiotic use.

Extra-label antibiotic therapy must be prescribed only in accordance with the Food, Drug, and Cosmetic Act and its

regulations.

In 1996, the Animal Medicinal Drug Use Clarification Act (AMDUCA) amendments to the Food, Drug and Cosmetic Act became federal law. This essentially legalized extra-label antibiotic use by veterinarians (not for producers). It defined the valid VCPR as discussed previously. Veterinarians in integrated poultry companies strive to use antibiotics at labeled indications and dosage. When prescribing extra-label use of antibiotics, a veterinarian performs it only in compliance with AMDUCA and its extralabel drug use regulation. **Veterinarians should work with those responsible for the care of poultry to use antibiotics judiciously regardless of the distribution system through which the antibiotic was obtained.**

Poultry producers are responsible for the production of poultry on their farms, however, information provided by live production mangers, veterinarians and/or best management practices that have been established by the National Chicken Council and National Turkey Federation should be followed. Veterinarians should work closely with producers, service technicians, service persons, and production managers to insure responsible use of therapeutic antibiotics. A veterinarian, however, should always be responsible for the initiation and evaluation of antibiotic therapy.

Regimens for therapeutic antibiotic use should be optimized using current pharmacological information and principles.

Continuing education programs by the American Veterinary Medical Association, American Association of Avian

Pathologists and technical updates from pharmaceutical technical service veterinarians, keep poultry veterinarians and managers up to date on current information regarding antibiotic use. Producers should use these individuals as resources regarding current information on antibiotic use.

Antibiotics considered important in treating refractory infections in human or veterinary medicine should be used in animals only after careful review and reasonable justification. Consider using other antibiotics for initial therapy.

Poultry veterinarians and producers should recognize the importance of antibiotic resistance in both human and veterinary medicine. Important antibiotics used in both poultry and humans are to be held in reserve to minimize the rate of resistance development to these important compounds.

Use narrow spectrum antibiotics whenever appropriate.

Antibiotics usually are either broad or narrow in their spectrum of activity. A broad-spectrum antibiotic tends to be active against a broader range of bacteria including both gram negative and gram positive organisms (i.e., bacteria that causes colibacillosis, cholera, etc) while narrow spectrum antibiotics are active against either gram positive (for example *Staphylococcus*) or gram negative (for example *E. coli*). Broad-spectrum antibiotics tend to lead to the development of resistance in bacteria that are **not** the ones involved in the infection you are treating. To minimize the development of broad-spectrum resistance, narrow spectrum, bactericidal antibiotics should be chosen when culture and sensitivity results suggest therapeutic success. Veterinarians will advise the producer in the use of the appropriate antibiotics.

Utilize culture and susceptibility results to aid in the selection of antibiotics when clinically relevant.

Before antibiotic therapy is initiated, based on mortality and

morbidity, some typically affected birds should be humanely euthanized and samples taken for bacterial culture and sensitivity testing. This can be performed at regional State diagnostic laboratories, universities or in integrated companies' diagnostic facilities. This is common practice in the poultry industry today. A poultry veterinarian uses this information to make informed decisions regarding the appropriate antibiotic therapy to be initiated. This information should be kept by the producer and veterinarian as part of the flock and farm history to determine changes in antibiotic susceptibility patterns on farms.

Therapeutic antibiotic use should be confined to appropriate clinical indications. Inappropriate uses such as for uncomplicated viral infections should be avoided.

Viral, fungal and other non-bacterial infections should not be treated with antibiotics. Producers and veterinarians should pay special attention to disease outbreaks to determine if, and when antibiotic therapy is warranted. Every effort should be made to address disease outbreaks with other disease management strategies prior to the initiation of antibiotic therapy.

Therapeutic exposure to antibiotics should be minimized by treating only for as long as needed for the desired clinical response.

Due to the cost of antibiotic use in poultry and limited availability of antibiotics in poultry, producers should work with veterinarians and service technicians to closely monitor antibiotic treatments and minimize antibiotic therapeutic exposure in flocks. Producers should use antibiotics according to labeled indications that include the treatment period. Any extra-label

use of antibiotics should be in accordance with a VCPR and within AMDUCA regulations. Producers should avoid prolonged use of antibiotics but should treat for a period sufficient to achieve the desired clinical outcome.

Limit therapeutic antibiotic treatment to ill or at risk animals, treating the fewest animals indicated.

In a poultry disease outbreak, all birds are not infected at the same time with the disease to which antibiotic therapy is warranted. However, birds in the same house are "at risk" to the same primary disease that results in secondary bacterial infections. Only birds within the same house that are ill or at risk should be treated. Producers should not treat adjacent houses that are not clinically affected with disease. If therapeutic antibiotic intervention isn't cost effective and a low number of birds are infected per house, the cost of treatment will usually dictate that no antibiotics be used at all.

Minimize environmental contamination with antibiotics whenever possible.

Every effort should be made to avoid environmental contamination with antibiotics. The cost of antibiotics generally ensures that the antibiotics be used specifically in the diseased flock and not introduced into the environment unnecessarily. Properly dispose of unused antibiotics.

Accurate records of treatment and outcome should be used to evaluate therapeutic regimens.

Record keeping is an integral part of the integrated poultry industry. Production records including medication costs,

evaluation and outcome are kept and placed in the history of the farm for future reference in determining any changing antibiotic susceptibility patterns. Producers should also maintain their own records of flock treatments (product used, date of use, duration of treatment, dosage, outcome of treatment, etc.) for future reference.

Conclusion: The overall goals of judicious therapeutic antibiotic use and the principles explained in the publication are: 1) to provide information to producers regarding the appropriate use of antibiotics in poultry; 2) minimize antibiotic resistance development; 3) minimize the transfer of resistant bacteria to humans; and, 4) provide insight and bring awareness to producers of the global problem of antimicrobial resistance. The producer and veterinarian should work closely when antibiotic therapy is needed in a flock and both must continue to work toward ensuring a safe food supply for consumers.

Other Sources of Information:

American Association of Avian Pathologists Guidelines for Judicious Therapeutic Antimicrobial Use in Poultry. American Association of Avian Pathologist. New Bolton Center.
382 W Street Road, Kennett Square, PA, 19348.
Phone: 610-444-4282.
(Also available at
http://www.avma.org/scienact/jtua/poultry/poultry00.asp)

National Chicken Council Drug Management Guide. National Chicken Council. 1015 Fifteenth Street NW, Suite 930.

Washington, DC 20005-2905. Phone 202-296-2622

National Turkey Federation Best Management Practices.
National Turkey Federation. Suite 400, 1225 New York Ave., NW
Washington, DC 20005; Phone 202-898-0100

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Veterinary Medicine
August 2001